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EVIDENCE FOR HEALTH CARE

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October 1 - Volume 138 - Number 5

Structural validity study:

- Structural validity of the Brazilian version of the Western Ontario and McMaster Universities Osteoarthritis Index among patients with knee osteoarthritis

Systematic review of comparative studies:

- Reverse-transcriptase polymerase chain reaction versus chest computed tomography for detecting early symptoms of COVID-19

Narrative review:

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Cochrane Library: the best evidence within everyone's reach

Maria Eduarda dos Santos Puga[I], Álvaro Nagib Atallah[II]

Cochrane Brazil, São Paulo (SP), Brazil

IMSc, PhD. Librarian, Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil; Director, Coordenadoria da Rede de Bibliotecas UNIFESP (CRBU), São Paulo (SP), Brazil. Information Specialist, Cochrane Brazil, São Paulo (SP), Brazil. orcid.org/0000-0001-8470-861X

IIMD, PhD. Full Professor and Head of the Discipline of Emergency Medicine and Evidence-Based Medicine, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil. Director of Cochrane Brazil, São Paulo (SP), Brazil. orcid.org/0000-0003-0890-594X

The Cochrane Library represents excellence in the production of systematic reviews, which are considered to provide the best evidence for diminishing uncertainties within healthcare. It is among the ten most important medical journals worldwide and is available to Brazilians openly and free of charge.[1-2]

Within the Cochrane Library, there is a collection of databases that provides evidence directed towards Cochrane systematic reviews and their protocols (Cochrane review in progress) and towards Cochrane database systematic reviews (CDSR). The Cochrane Library also includes the largest directory of clinical trials in the world (CENTRAL, the Central Register of Controlled Trials) and Cochrane Clinical Answers, which is an integrated search resource that enables searches in external databases, all within the same tool.[3]

Cochrane reviews are live publications, given that they are updated every two years. The Cochrane Library offers its users the best two levels of evidence for decision-making within healthcare.

HOW TO ACCESS IT

The web address https://www.cochranelibrary.com/ provides free access to the Cochrane Library. All that is needed is an internet connection.

HOW TO DO SEARCHES

All production within the Cochrane Library is indexed using the controlled terminology of Medical Subject Headings (MeSH). One useful tip for starting a search is to try to organize it using the acronym **PICO** (**P:** problem/population; **I:** intervention; **C:** control; **O:** outcome). This will be helpful in implementing the search.

Search terms can also be identified through the Portuguese-language official vocabulary of the Descritores em Ciências da Saúde (DECS), which is available from https://decs.bvsalud.org/. From this, the equivalent English-language terms can be copied into each element of **PICO**.

In the Cochrane Library, it is unnecessary to use **T** (type of study) or, as seen in some search-organizing acronyms, **S** (study design), given that searches will find systematic reviews, review protocols and clinical trials. Cochrane searches are already filtered to show these top two levels and syntheses of evidence.

SIMPLE SEARCH

One or more words representing the subject of interest can be entered. The result will identify these words as they appear in article titles, abstracts or keywords (**Figure 1**). Example: low back pain and acupuncture (P - **Low Back Pain**; I - **Acupuncture**) (**Figure 2**).

RESULT FROM SIMPLE SEARCH

The result obtained is presented in terms of directories (filters): Cochrane reviews; followed by Cochrane protocols; reviews registered in the Cochrane database that are in progress; trials, comprising clinical trials gathered in the main databases; and lastly, manual searches through Cochrane centers and groups. These can be viewed by clicking on the different tabs of the results (**Figure 3**).

ADVANCED SEARCH

The entire Cochrane Library collection is indexed using the MeSH vocabulary. The terms in English can be located via DECS to build up a PICO framework. The Medical Terms (MeSH) tab is then accessed, as indicated in **Figure 4**, and the term in English can then be entered (**Figure 5**).

In the advanced search format, the MeSH term is then located and selected (**Figure 6**), so that the search will be performed using the official terms. This is done for all the terms used in building up the PICO, by clicking on the **Select** button and then on **Add search manager**. It is important to do this for all the terms in the PICO.

The **Search manager tab** is then accessed, which provides the result for each MeSH term identified.

Intersections between terms can be managed here to obtain the final result. The databases use Boolean operators (OR, AND and NOT). Therefore, in an advanced search strategy, it needs to be specified whether intersections between sets of terms exist (**Figure 7**).

Figure 7 shows the result from each set of terms (#) investigated and also the intersections between sets (#). Set #3 shows an intersection, using AND: #1 AND #2 (**Figure 8**). By clicking on any of the results, a screen with the data retrieved will appear (**Figure 9**).

Figure 1. Initial interface for Cochrane search.

Figure 2. Simple search just using words.

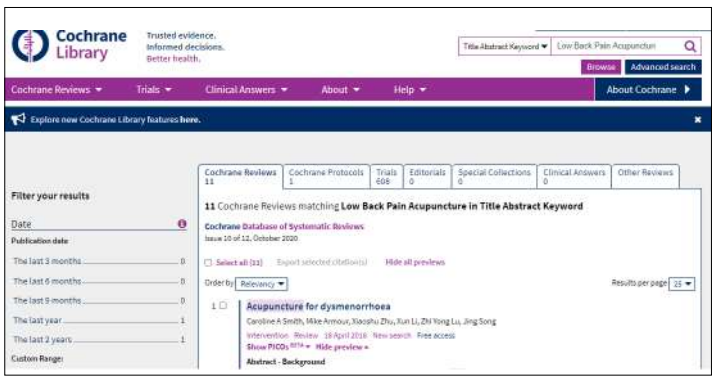

Figure 3. Result from simple search.

Figure 4. Search using MeSH terms.

Figure 5. Selection of tab for MeSH terms in advanced search.

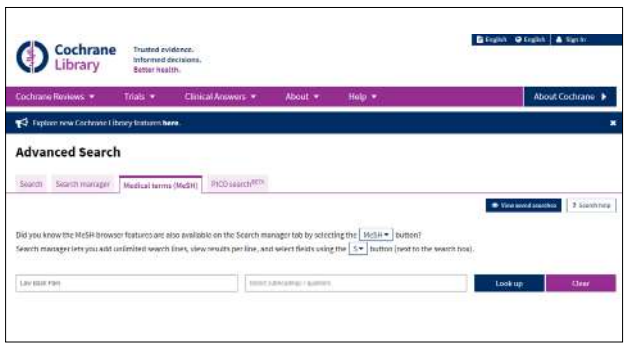

Figure 6. Identification of MeSH terms, which are then loaded into the search strategy.

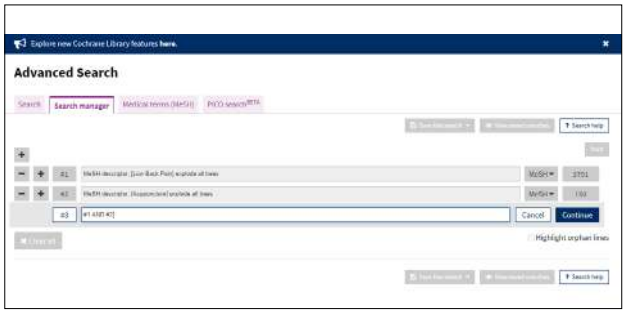

Figure 7. Advanced search strategy.

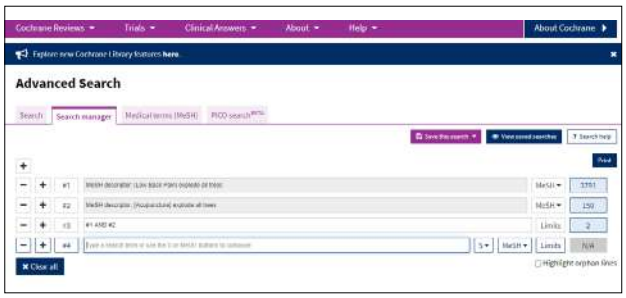

Figure 8. Result from advanced search for each MeSH term.

Figure 9. Result from advanced search, with intersection of sets #.

Figure 10. COVID-19 special collection.

Figure 11. COVID-19 special collection: critical care translated into Portuguese.

The special collections of the Cochrane Library have contributed to publication of a series of robust collections that provide open access to systematic reviews supporting prevention and treatment of COVID-19 (**Figure 10**). These collections have been translated into several languages, including Portuguese (**Figure 11**).

The Cochrane Library app is an instrument or resource that allows all healthcare professionals to follow the most recent evidence from Cochrane reviews easily and rapidly. It can also be used for offline reading of the material. Thus, healthcare professionals can create a personal collection of evidence so as to be able to make decisions assertively, from the highest quality of evidence available in the literature.

In Brazil, through funding from the Coordination Office for Improvement of Higher-Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES), the Cochrane Library is accessible to everyone, without exception.

The Brazilian Cochrane Center was founded by Dr. Álvaro Nagib Atallah in 1996 and was inaugurated by Dr. Iain Chalmers. It functions as a training center for undergraduate and postgraduate students at the Federal University of São Paulo (Universidade Federal de São Paulo) and other Brazilian universities, and it is open to everyone with an interest in this. It produces systematic reviews for the Cochrane Library, Brazilian Ministry of Health and specialist medical societies, and produces technological assessments of public interest, without conflicts of interest.

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Address for correspondence:
Álvaro Nagib Atallah
Cochrane Brasil
R. Borges Lagoa, 564
Vila Mariana — São Paulo (SP) — CEP 04038-001
Tel. (+55 11) 5571-4721/5575-2389
E-mail: atallahmbe@uol.com.br

Diagnostic discrepancies between emergency department admissions and hospital discharges among older adults: secondary analysis on a population-based survey

Thiago Junqueira Avelino-Silva[I], Michael Alan Steinman[II]

University of California San Francisco, San Francisco (CA), United States

[I]MD, PhD. Physician and Adjunct Professor, Division of Geriatrics, Department of Internal Medicine, Hospital das Clinicas (HC), Faculdade de Medicina FMUSP, Universidade de São Paulo; Vice-Director, Laboratorio de Investigacao Medica em Envelhecimento (LIM-66), Division of Geriatrics, Hospital das Clinicas, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo (SP), Brazil.
orcid.org/0000-0001-9347-0519

[II]MD. Physician and Professor of Medicine, Division of Geriatrics, Department of Medicine, University of California San Francisco (UCSF), San Francisco (CA), United States; Professor of Medicine, San Francisco Veteran Affairs Medical Center, San Francisco (CA), United States.
orcid.org/0000-0002-9564-9480

KEY WORDS (MeSH terms):
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Diagnosis.
Emergency medicine.
Hospital medicine.
Diagnostic errors.
Patient safety.

AUTHORS' KEY WORDS:
NHAMCS.
Atypical presentation.
Clinical assessment.

ABSTRACT

BACKGROUND: Older adults frequently experience nonspecific clinical features. However, there is limited evidence on how often admission diagnoses for hospitalized older patients are incorrect, potentially leading to treatment delays.

OBJECTIVES: To determine the consistency between hospital admission and discharge diagnoses, and identify factors associated with diagnostic discrepancies in older adults.

DESIGN AND SETTING: Population-based cohort study in the United States. We included adults aged ≥ 18 years who were admitted from emergency departments (EDs) to hospitals, identified using the 2005-2010 National Hospital Ambulatory Medical Survey, a nationally representative survey.

METHODS: Three admission diagnoses and the principal discharge diagnosis were captured and classified as discrepant if they involved considerably different conditions within the same organ system, or different organ systems altogether.

RESULTS: Each year, 12 million adults were hospitalized following ED visits in the United States; 45% were aged ≥ 65 years. These patients' mean age was 79 years and 58% were women. Diagnostic discrepancies between admission and discharge were more common among adults ≥ 65 years (12.5 versus 8.3%; P < 0.001). Certain admission diagnoses had particularly high rates of diagnostic discrepancies: 26-27% of patients presenting with mental disorders or with endocrine and metabolic diseases had substantial diagnostic discrepancies between admission and discharge. Substantial diagnostic discrepancy was independently associated with longer hospitalization and higher in-hospital mortality.

CONCLUSION: One out of eight older adults hospitalized from EDs was discharged with a principal diagnosis differing considerably from the admission diagnosis. Given that missed or delayed diagnoses are a critical safety problem, clinicians should be vigilant and frequently cogitate alternative diagnostic possibilities.

INTRODUCTION

Emergency department (ED) visits by patients aged 65 and older have steadily increased over the past decade.[1] Moreover, there has been a substantial increase in the intensity of resource utilization among older adults, including hospital admissions, intensive care unit admissions, return visits and readmissions, and use of advanced imaging and laboratory tests.[1,2] This is explained not only by the aging of the population, but also by the fact that older adults often have complex conditions aggravated by multiple comorbidities, polypharmacy, functional impairment and cognitive decline.[3-6]

Diagnosis and treatment are further complicated because such patients might present atypical signs and symptoms of disease, thus increasing the degree of clinical uncertainty involving their cases.[3,7] Emergency physicians have reported feeling inadequately trained to address geriatric issues and having greater difficulty when managing older adults with diverse clinical presentations.[8,9] Previous research findings indicate that older adults are at higher risk of missed diagnoses.[2] In a study including 103 individuals aged 65 years or more, conducted by Caterino et al., up to 18% of older patients diagnosed with infection during an ED stay were not subsequently diagnosed as infected after admission.[10] Likewise, Thomas et al. observed in a cohort of 102 elderly subjects that at least a third of the patients clinically diagnosed with dehydration at admission were not dehydrated.[11]

Despite such concerns, these previous studies have generally focused on misdiagnosis of specific clinical conditions. Given that they came from single hospitals or limited samples, their generalizability is uncertain. In summary, there is limited knowledge about how diagnostic uncertainty affects older patients' care, or how often the admission diagnosis for hospitalized older adults turns out to be incorrect.[12] This is an important gap because missed or delayed diagnoses might give rise to major risks regarding patient safety. A patient's diagnosis at the time of admission prompts the initial course of treatment and, if inaccurate, may lead to wasting valuable time on unnecessary measures, while critical ones are neglected.[13] Understanding the broader epidemiology of this phenomenon and identifying its risk factors could raise the awareness of front-line healthcare professionals regarding the complexities of caring for older adults and might consequently improve their ability to provide timely and adequate treatment.

OBJECTIVES

We used nationally representative data from the United States to better understand diagnostic discrepancies in older adults, through evaluating the incidence of substantial diagnostic discrepancies between hospital admission and discharge among these patients, compared with subjects aged 18 to 64. We further aimed to identify potential risk factors associated with occurrences of diagnostic disagreements relating to older adults, and to assess whether such events were associated with unfavorable outcomes in this population.

METHODS

Study design and population

This was a secondary analysis on data collected from the 2005-2010 National Hospital Ambulatory Medical Survey (NHAMCS). NHAMCS data are annually collected and generated through a multistage sample design that provides a national probability sample of ED visits made to non-federal, general and short-stay hospitals.[14] It identifies primary sampling units across the country, then sampling hospitals within each primary sampling unit and, finally, visits to these locations' emergency services. Trained hospital employees abstract the data using standardized entry forms, which varied little from 2005 to 2010.

The 2005-2010 NHAMCS datasets include information from 208,956 ED records representing 740 million encounters. We analyzed the incidence of diagnostic discrepancies among adults aged 18 or over who were admitted from EDs to hospitals and restricted our detailed analysis of risk factors to the population of adults aged 65 years or more. We excluded ED visits that did not lead to hospitalization, ED deaths and patients younger than 18 years of age.

Study protocol and definitions

The NHAMCS database contains fields for up to three ED physicians' diagnoses (one primary and two secondary) and for one principal hospital discharge diagnosis, which are coded in accordance with the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM). Diagnoses are abstracted from information on medical records (not from billing information).

Exclusion of nonspecific diagnoses

We compared the diagnoses at hospital admission and hospital discharge with the goal of identifying diagnostic discrepancies between reasonably specific admission and discharge diagnosis. For this reason, we sought to remove from consideration diagnoses that were nonspecific (e.g. "chest pain", "altered mental status" or "cough"), since these often represent diagnostic uncertainty and are more difficult to interpret. Similarly, we sought to exclude conditions captured in ICD-9 codes that were not truly disease diagnoses (e.g. "abnormal blood chemistry" or "psychiatric examination"). In order to accomplish these exclusions in a systematic manner, ICD-9-CM codes were independently reviewed and classified in accordance with the following categories: (a) diseases and disease processes; (b) organ system-specific symptoms and signs; (c) general/nonspecific symptoms and signs; or (d) test results and procedures. A blinded, experienced third evaluator acted as adjudicator when necessary. Cases in which all the admission diagnoses or the discharge diagnosis were classified as (c) general/unspecific symptoms and signs or (d) test results and procedures were excluded from the analysis, as were records in which diagnostic information was missing from all admission fields or the discharge field (**Table 1**).

Identification of diagnostic discrepancies

We used an automated two-stage process followed by individualized review of the cases, to identify diagnostic discrepancies (**Figure 1**). Firstly, we classified the diagnoses using the multilevel diagnoses of the clinical classification software for ICD-9-CM.[15] This software categorizes ICD-9-CM codes into clinically relevant groups. It aggregates diagnoses following a hierarchical coding system based on the type of disease, in which the top level generally corresponds to an organ system (e.g. diseases of the digestive system), the second level corresponds to broad types of disease within that organ system (e.g. intestinal infection or upper gastrointestinal disorders) and the third and fourth levels correspond to more specific disease states.

We defined admission and discharge diagnoses as probably discrepant when the discharge diagnosis did not match any of the admission diagnoses at the second level of the clinical classification software coding system, i.e. the discharge diagnosis was not

Table 1. Examples of how the diagnoses were classified

Admission diagnostic category 1	Admission diagnostic category 2	Admission diagnostic category 3	Discharge diagnostic category	Classification	Justification
Chest pain	Respiratory abnormality	Pulmonary congestion	Chest pain	**Excluded**	All diagnoses are non-specific
Ulcer of lower limb	Cellulitis of leg	Brain injury	Cellulitis of leg	**No diagnostic change**	Same diagnosis
Bipolar disorder	Lack of housing	Depressive disorder	Schizoaffective disorder	**Change to closely related diagnostic category**	Similar disease process, same organ system
Intermediate coronary syndrome	Thrombosis of lower extremities	-	Esophageal reflux	**Change to distantly related diagnostic category**	Different disease process, reasonable differential diagnosis
Closed fracture of patella	Head injury	Pneumonia	Cerebral infarction	**Change to unrelated diagnostic category**	Different disease process, different organ system

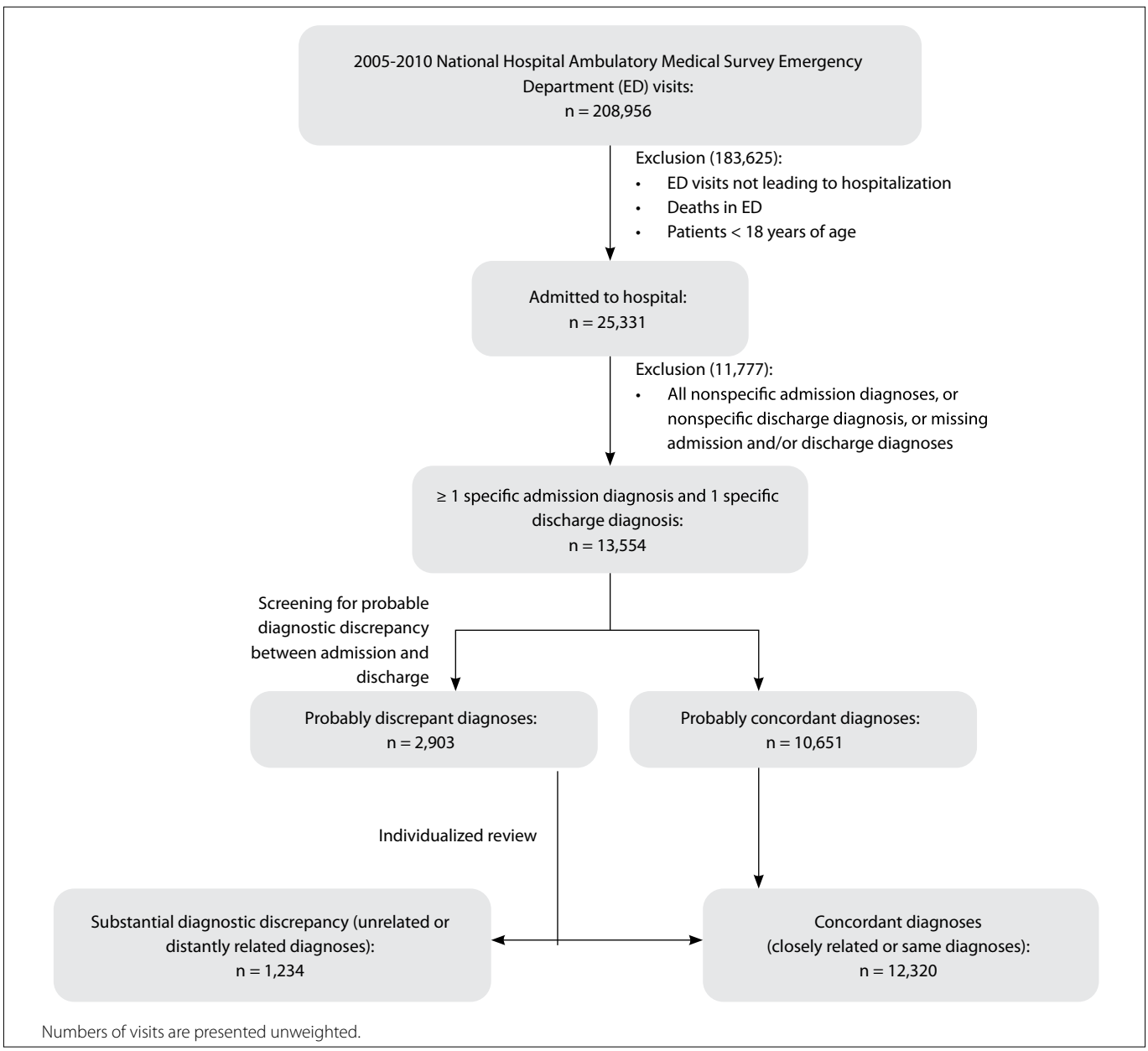

Figure 1. Study design flowchart.

within the same broad class of diseases within an organ system as any of the admission diagnoses.

Probable diagnostic discrepancies identified based on the second level of the clinical classification software could still represent ICD-9-CM diagnoses that were in reality similar and not grouped together due to coding inconsistencies. Accordingly, the cases were individually assessed and classified by an experienced clinician using a modified version of the Rating Scale for Diagnostic Change,[16] which is an instrument designed to classify the degree of concordance between diagnoses over time. By comparing the discharge diagnosis with the closest matching specific admission diagnosis, we classified the diagnosis as follows (**Table 1**): (1) no category change (the discharge diagnosis referred to the same disease process, with alterations only in wording or specificity); (2) change to a closely related diagnostic category (the discharge diagnosis referred to a different disease process in the same organ, or to a similar disease process in the same system); (3) change to a distantly related category (the discharge diagnosis referred to a different disease process but considered a reasonable differential diagnosis); or (4) change to an unrelated category (the discharge diagnosis referred to a different disease process and different organ system, in comparison with the admission diagnosis). We defined "substantial diagnostic discrepancy" as present when the admission and discharge diagnoses were classified as distantly related (category 3) or unrelated (category 4), or absent in other situations. A second experienced investigator independently reviewed and classified a sample of the cases to assess inter-rater agreement for substantial diagnostic discrepancy, which was 92%. The authors were blinded to all remaining covariates when completing this task.

Predictors and outcomes of significant diagnostic discrepancy

We evaluated potential risk factors for substantial diagnostic discrepancy among patients aged 65 and over, including age, sex, race/ethnicity, nursing home residence, triage acuity, ED visit in the last 72 hours, hospital discharge within past seven days, presenting diagnosis, pain level, vital signs, level of consciousness at admission, number of ED diagnostic and screening tests, ED length of visit, and length of hospital stay, each of which were recorded on the NHAMCS survey form. Lastly, we investigated the association between substantial diagnostic discrepancy and in-hospital mortality among these patients.

Statistical analysis

We used the NHAMCS recommended procedures to adjust for the complex survey design and weight the sample to generate nationally representative estimates, with 95% confidence intervals based on standard errors also specified by NHAMCS.[17] A descriptive analysis was performed using estimated means and proportions, and groups were compared using adjusted Wald tests or designed-based F tests as applicable for continuous or categorical variables, respectively. A multivariate analysis was accomplished using backwards-stepwise logistic regression, including demographic and clinical variables that were statistically associated with substantial diagnostic disagreement in the univariate analysis ($P < 0.1$) and/or were hypothesized to be conceptually relevant to the model. Missing data were handled using multiple imputation methods. The statistical analyses were performed using Stata 13.1 (Stata Corp, College Station, TX, United States).

Because the datasets are publicly available and contain no patient identifiers, the study was approved as exempt by the institutional review board of the University of California San Francisco and the San Francisco Veteran Affairs Medical Center, on November 15, 2014 (study 14-15031; reference 122992).

RESULTS

The 2005-2010 NHAMCS datasets included 208,956 unique records, representing an estimated 740 million ED visits in the United States. An estimated 72 million adults were admitted from EDs, of whom 45% were aged 65 years or more. The mean age in this group was 79 years and 58% were women (**Table 2**). Approximately 19% of the visits by hospitalized patients in all age groups were excluded because of missing diagnostic information, and an additional 27% were excluded due to non-specific diagnostic codes. The proportions of missing and nonspecific diagnoses did not differ between age groups (respectively, $P = 0.21$ and $P = 0.78$).

Among all the adults included, 10.2% presented substantial diagnostic discrepancy from admission to discharge. The rate of substantial diagnostic discrepancy increased with advancing age (**Figure 2**). Overall, 12.5% of the patients aged 65 years or older had substantial diagnostic discrepancy versus 8.3% of those aged 18 to 64 ($P < 0.001$). The subsequent analyses focus on the older age group.

The relationship between demographic and clinical characteristics and having substantial diagnostic discrepancy is shown in **Table 2**. Patients were more likely to have substantial diagnostic discrepancy when the admission diagnoses referred to diseases of the genitourinary system, mental illnesses, endocrine and metabolic diseases, or diseases of the musculoskeletal system. Patients admitted with diseases of the respiratory system or injuries were less likely to have discrepancies. The three most frequent admission diagnoses that were discrepant, compared with the discharge diagnosis, were urinary tract infection (10% of all discrepant admission diagnoses), pneumonia (7%) and congestive heart failure (7%) (data not shown in tables).

Length of stay was greater in hospitalizations with substantial diagnostic discrepancy (median 5 days; interquartile

range = 3-7 days) than in those without substantial diagnostic discrepancy (median 4 days; interquartile range = 2-5 days; P < 0.001), as was mortality (26 versus 12%; P < 0.001). Other characteristics that were found to be more frequent among patients with substantial diagnostic discrepancy included the following: residing in nursing homes, having altered levels of consciousness, presenting lower levels of mean arterial pressure and having more ED diagnostic and screening tests.

In a multivariate analysis model that included demographic and clinical covariates, we found that age, nursing home residence, altered level of consciousness, mean arterial pressure, number of ED diagnostic and screening tests and length of stay were

Table 2. Older adults' characteristics, and factors associated with substantial diagnostic discrepancy between admission and discharge diagnoses, National Hospital Ambulatory Medical Survey (NHAMCS), 2005-2010 (n = 5,767)[a]

	Weighted proportion, %	Substantial diagnostic discrepancy, %	Adjusted odds ratio	(95% CI)
Demographic data				
Age (years)			1.02[e]	(1.01-1.04)
65-74	35	10		
75-84	40	13	1.37	(1.05-1.78)
85 or more	25	15	1.53	(1.16-2.01)
Female	58	12	0.94	(0.76-1.17)
Non-Hispanic/Latino	93	13	0.99	(0.68-1.43)
Race				
White	84	12		
Black	12	12	0.98	(0.72-1.37)
Other	4	14	0.99	(0.67-1.43)
Nursing home resident[b]	15	18	1.37	(1.04-1.81)
Clinical data				
Discharged from hospital within last 7 days[d]	5	15	1.23	(0.78-1.94)
Triage acuity[c]				
Emergency	35	13	1.23	(0.85-1.76)
Urgent	51	12	1.15	(0.83-1.59)
Semi-urgent/ Non-urgent	14	11		
Altered level of consciousness[d]	9	17	1.32	(1.02-1.88)
Pulse < 60 or ≥ 100 beats/min[b]	30	13	1.03	(0.81-1.31)
Respiratory rate ≥ 20 insp/min[b]	35	12	0.89	(0.69-1.16)
Mean arterial pressure < 90 mmHg[b]	37	15	1.32	(1.07-1.62)
Temperature < 97 °F or ≥ 101 °F[b]	17	15	1.13	(0.86-1.49)
Number of diagnostic/ screening tests in ED ≥ 7[b]	63	13	1.04[e]	(1.01-1.07)
Hospital stay ≥ 7 days[b]	30	16	1.03[e]	(1.01-1.04)
Death[b]	3			
Presenting diagnosis				
Diseases of the circulatory system	30	11	0.9	(0.7-1.1)
Diseases of the respiratory system	20	10	0.7	(0.5-0.9)
Diseases of the digestive system	13	10	0.8	(0.6-1.1)
Injury and poisoning	12	7	0.5	(0.3-0.8)
Diseases of the genitourinary system	8	20	1.7	(1.2-2.3)
Infectious and parasitic diseases	3	22	1.5	(0.9-2.5)
Mental illness	3	27	2.8	(1.6-4.7)
Diseases of the skin and subcutaneous tissue	3	18	1.4	(0.8-2.4)
Neoplasms	2	17	1.5	(0.8-2.9)
Endocrine, nutritional and metabolic diseases	2	26	2.9	(1.9-4.5)
Diseases of the musculoskeletal system and connective tissue	2	20	2	(1.1-3.6)
Diseases of the blood/ blood-forming organs	1	20	1.8	(0.6-4.9)
Diseases of the nervous system/ sense organs	1	12	1	(0.4-2.6)

95% CI = 95% confidence interval; ED = emergency department.

[a]Because adjusting for the complex survey design makes raw numbers (N) not directly proportional to weighted percentages, we present only weighted percentages; Data missing/ unknown: [b]< 10%; [c]10%-19%; [d]≥ 20%; [e]Per each additional unit (year; test; day).

independently associated with substantial diagnostic disagreement (**Table 2**). In addition, substantial diagnostic discrepancy was independently associated with in-hospital mortality (odds ratio = 2.2; P = 0.001), after adjusting for demographic and clinical covariates.

Because we excluded nonspecific diagnoses from consideration, our methods had the potential to misclassify certain patients as having substantial diagnostic discrepancy. For example, consider a patient with admission diagnosis #1 of urinary infection, admission diagnosis #2 of chest pain, and discharge diagnosis of acute myocardial infarction. In this case, the admission and discharge diagnoses would be classified as substantially discrepant because the nonspecific diagnosis "chest pain" would not be used for the comparison, and the remaining admission diagnosis (urinary infection) would be considered discrepant from the discharge diagnosis of acute myocardial infarction. We thus performed a conservative sensitivity analysis including only the records in which all of the admission diagnoses, as well as the discharge diagnosis, were specific. In this sensitivity approach, 5% of the patients aged 18-64 years had substantial diagnostic discrepancy versus 9% for those aged 65 years or more (P < 0.001).

DISCUSSION

One out of eight older adults hospitalized from EDs in the United States with a specific admission diagnosis was discharged with a substantively different principal diagnosis. Diagnostic discrepancies were more common among older adults, occurring in 12.5% of adults over the age of 65 years, with a particularly high rate among patients aged 85 years or more (14.5%), while appearing in only 8.3% of those under 65 years. Moreover, substantial diagnostic discrepancy was independently associated with longer hospital stays and increased in-hospital mortality. Presenting clinical diagnosis, nursing home residence, lower mean arterial pressure and more ED diagnostic and screening tests were also independently associated with substantial diagnostic discrepancy.

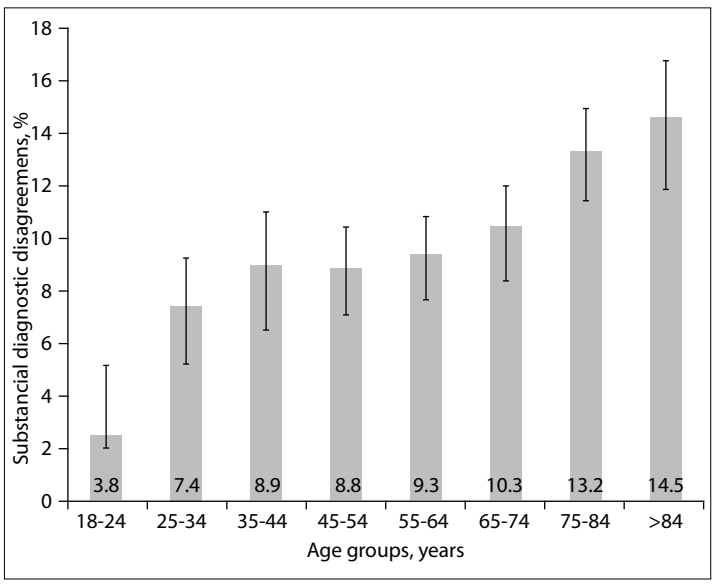

Figure 2. Weighted proportion of visits with substantial diagnostic discrepancy, according to age groups.

Missed, delayed or incorrect diagnoses are estimated to occur in 5% to 20% of medical encounters.[18,19] Older age is generally thought to be associated with diagnostic uncertainty and is therefore a risk factor for diagnostic errors, but the data reported so far have mostly been restricted to specific settings or clinical conditions such as malpractice claims, cancer, infections and myocardial infarction.[11,20-23] In a study conducted in a university hospital, 230 patients (32%) admitted from the ED were discharged with diagnostic changes in relation to specificity and/or category, and this occurred more frequently among older patients.[16] Another study that investigated ED admission-to-discharge discrepancies in an urban level-1 trauma hospital reported that the majority of the group with diagnostic disagreements comprised elderly people.[24] To the best of our knowledge, ours was the first study to analyze this issue in a nationally representative sample of ED encounters and confirm that older age was associated with greater rates of admission-to-discharge diagnostic discrepancies.

The frequency of diagnostic discrepancies varied according to the presenting clinical diagnosis at admission. It is intriguing that substantial diagnostic discrepancy tended to be less likely to happen with the most frequent conditions, while less frequent illnesses were associated with its occurrence. Nevertheless, other studies have shown that a broad range of clinical conditions is frequently misdiagnosed, with similar patterns of individual and systemic vulnerabilities contributing to failures in diagnostic processes.[24,25] Therefore, preventive measures that focus on addressing such systematic issues would likely have a more significant impact than those targeting specific diseases.

Discrepancies were also associated with factors potentially indicative of clinical severity, such as lower arterial blood pressure, altered level of consciousness and longer ED visits. It is plausible that patient characteristics contributing to clinical complexity increase the difficulty of establishing definite diagnoses. In a study on 307 closed malpractice claims alleging missed or delayed diagnosis in the ambulatory setting, Gandhi et al. reported that patient-related factors contributed to the errors in 46% of the cases.[25] These included atypical clinical presentation and complicated medical history in 15% and 10% of the cases, respectively. However, most problems were also linked to cognitive factors relating to the care provider, such as clinical judgment and knowledge breakdowns.

Interestingly, substantial diagnostic discrepancy was also associated with the use of more diagnostic and screening tests in the ED. Although it is reasonable to infer that this is a consequence of greater clinical insecurity, complexity and severity in these cases, it

is significant that these tests did not prevent substantial diagnostic discrepancy from happening after the admissions. This finding is consistent with previous reports suggesting that the rate of misdiagnosis has remained constant over the past decades notwithstanding all the technological advances that have been witnessed in the field of medicine.[24,26] Accurate diagnosis still appears to be mostly dependent on the quality of patient histories and physical examinations.

Given the challenges that geriatric patients involve, it might be helpful to develop training programs to educate care providers regarding geriatric syndromes and possible atypical clinical presentations in this population. Specific policies for older adults allowing for more time for medical evaluations could also prove helpful.

Patients with diagnostic discrepancies had 25% longer hospital stays and more than twice the mortality. Johnson et al. found similar results in the general medicine units of a university hospital, and reported that patients admitted from the ED had 15% longer stays when disagreements were identified.[13] It is important to note that not all diagnostic discrepancies in our study were necessarily due to misdiagnosis at the time of admission. Some of them may have been accounted for by new clinical conditions that arose during the hospitalization (i.e. nosocomial infections or new cardiovascular events, etc.), or even by poor documentation of critical diagnostic information. However, previous hospital-wide research has indicated that particularly high rates of diagnostic errors occur in the ED,[27] and it is reasonable to assume that at least a proportion of the disagreements that we discovered were due to misdiagnosis. Lastly, a previous study that reviewed medical records in detail and analyzed discrepancies between primary ED admitting diagnosis and primary discharge diagnosis concluded that such inconsistencies could be used reliably to screen for missed diagnoses.[24]

In many cases, diagnoses can be elusive and wrong, even in the setting of good clinical care, especially when providing care for older adults who might have several concomitant chronic and acute conditions. We excluded from our analyses the cases that only had nonspecific admission and/or discharge diagnoses, in an attempt to minimize the effects of diagnostic uncertainty and diagnostic codes that would retrieve discrepancies merely due to lack of specificity. This strategy probably contributed towards underestimating the degree of diagnostic uncertainty and change that actually occurred. Conversely, aspects of our methods may have contributed towards overestimating the rate of diagnostic discrepancies through discounting any information available from nonspecific diagnoses, as explained in our sensitivity analysis. Although limitations to coding and to how the comparisons were defined made it difficult to establish a single precise "true" rate of diagnostic discrepancies, our main analyses and the sensitivity analysis were generally consistent. Hence, these analyses allowed us to: (1) provide information on the magnitude of diagnostic discrepancies among patients with at least one specific admission diagnosis; and (2) indicate that there was a large proportion of patients with non-specific admission diagnoses for whom diagnostic uncertainty and the possibility for discrepancies were even greater.

There were other limitations to this study, including its retrospective nature and imperfect measurement of potential confounders, along with the probability sample design of the NHAMCS dataset. Although the data collectors underwent training and the data were subject to a 10% random sample crosscheck, occurrences of residual errors in collection and coding cannot be ruled out. Specifically, regarding our study, the dataset had a restricted number of diagnostic variables and limited clinical information. Nonetheless, this dataset has strength as a nationally representative sample and has been widely used in similar analyses.[28-30]

CONCLUSIONS

Missed and delayed diagnoses among older adults represent a critical patient safety problem, and diagnostic procedures are becoming increasingly complex and susceptible to failure.[25] They are a leading cause of malpractice claims and preventable adverse events in hospitals, and frequently result from failure to hypothesize the correct diagnosis.[21,22,31] Our results show that substantial admission-to-discharge diagnostic discrepancies occur more commonly among older adults hospitalized from the ED. These discrepancies may have occurred as a result of diagnostic error, coexistence of multiple conditions or development of new diseases. All of these possibilities have practical implications, and clinicians attending hospitalized older patients should be vigilant and consider alternative diagnostic possibilities early in the course of hospitalization. Future research should focus on interventions that might improve diagnostic practices for these patients, including geriatric training for in-hospital care providers and development of clinical decision support tools.

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Address for correspondence:
Thiago Junqueira Avelino-Silva
Hospital das Clínicas (HC), Faculdade de Medicina da Universidade de São Paulo (FMUSP)
Av. Dr. Enéas de Carvalho Aguiar, 155 — 8ª andar — Secretaria da Departamento de Clínica Médica, LIM-66
Sao Paulo (SP) — Brasil
CEP 05403-000
Tel. (+55 11) 2661-6236
E-mail: thiago.avelino@usp.br

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Characterization of prenatal healthcare for implementation of congenital toxoplasmosis surveillance program: cross-sectional study

Aline do Nascimento Benitez[I], Jancarlo Ferreira Gomes[II], Milenne Ura Seixas Santos Dias[III], Italmar Teodorico Navarro[IV], Regina Mitsuka-Breganó[V], Katia Denise Saraiva Bresciani[VI]

School of Veterinary Medicine, Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP), Araçatuba (SP), Brazil

[I]MSc, PhD. Veterinarian, Specialist in Zoonoses and Public Health and Postdoctoral Student, Postgraduate Program on Child and Adolescent Health, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
orcid.org/0000-0002-0770-9552

[II]MSc, PhD. Parasitologist, Specialist in Public Health and Professor, Postgraduate Program on Child and Adolescent Health, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
orcid.org/0000-0002-2466-7315

[III]RN. Nurse, Specialist in Occupational Health and Regional Director, Group XI (GVE), "Prof. Alexandre Vranjac" Epidemiological Surveillance Center, State Health Department of São Paulo, Araçatuba (SP), Brazil.
orcid.org/0000-0003-1578-3952

[IV]MSc, PhD. Parasitologist, Specialist in Zoonoses and Public Health and Professor, Department of Preventive Veterinary Medicine, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil.
orcid.org/0000-0001-9518-1083

[V]MSc, PhD. Parasitologist, Specialist in Zoonoses and Public Health and Professor, Department of Preventive Veterinary Medicine, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil.
orcid.org/0000-0002-6585-730X

[VI]MSc, PhD. Parasitologist, Specialist in Zoonoses and Public Health and Professor, Department of Animal Production and Health, School of Veterinary Medicine, Universidade Estadual Paulista (UNESP), Araçatuba (SP), Brazil.
orcid.org/0000-0002-8767-8855

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ABSTRACT

BACKGROUND: Prenatal toxoplasmosis remains a neglected disease worldwide and few government programs focusing on its prevention are available. Success in these programs has been extensively reported in the literature, yet the strategies used for their implementation, as a model for such actions in different communities, have not been described.

OBJECTIVES: To describe the aspects of prenatal care strategies in 13 municipalities within the regional healthcare unit of Araçatuba, in the northwestern region of the state of São Paulo in 2017, focusing on congenital toxoplasmosis.

DESIGN AND SETTING: Descriptive study on prenatal healthcare within the Brazilian National Health System, in 13 participating municipalities.

METHODS: Data on serological tests, referral clinics, notifications, healthcare strategies, health education and drugs for infected children were requested through a questionnaire that was sent via e-mail to people responsible for healthcare services in these municipalities.

RESULTS: Major differences relating to diagnoses, reference outpatient clinics, notifications, health education and healthcare and drugs for infected children were reported among the prenatal strategies of these 13 municipal healthcare services.

CONCLUSIONS: The lack of standardized prenatal strategy in the study area may compromise the prevention of infection. However, our identification of each aspect of prenatal care corroborates the need to implement a healthcare surveillance program relating to congenital toxoplasmosis.

INTRODUCTION

The transmission routes for toxoplasmosis include consumption of raw foods, undercooked meats and untreated water; contact with soil contaminated with the evolutionary infective forms of the protozoon *Toxoplasma gondii* (*T. gondii*); and transplacental infection.[1] Differences in pregnant women's food intake and cultural habits around the world are responsible for variations in the prevalence of congenital toxoplasmosis among countries,[2] and between communities within the same nation.[3] Preventive measures are common to all populations, since they concentrate on health education and early detection of infection during pregnancy.[4] However, the public health strategies for prevention of this parasitosis need to be appropriate for each situation.

T. gondii infection is a major problem within gestational health because of the possibility of irreversibly damaging the fetus.[1] The main types of damage reported have included chorioretinitis, deafness, intracranial calcification, microcephaly, hydrocephalus, seizures and intellectual disability. In addition, occurrences of spontaneous abortions, neonatal death and neurodevelopmental disorders have been recorded.[5]

Researchers from the World Health Organization (WHO) reported that in 2010, despite neglect due to little attention given to the prevalence, prevention and treatment of toxoplasmosis, 10.3 million cases of this disease were recorded worldwide, with 825,000 Disability-Adjusted Life Years (DALYs), one of the highest among foodborne parasitic diseases.[2]

The Brazilian strains of *T. gondii* are highly damaging to the eye tissue, in comparison with strains in other countries.[6] However, reduction of the incidence of congenital infection, through early identification of maternal infection and adoption of strategic therapy for pregnant women and

newborns up to one year of age, has been observed.[7] In Switzerland, three decades of serological monitoring of pregnant women led to an 85% reduction in the incidence of congenital toxoplasmosis.[8] Similar results have been found in other countries such as France[9] and Austria.[10]

Technical and scientific standards for promotion, protection and recovery of health have been developed within the Brazilian National Health System (Sistema Único de Saúde, SUS). SUS has the mission of promoting public health actions to ensure conditions of physical, mental and social wellbeing for the entire population. This is implemented by the Brazilian Ministry of Health and by the state and municipal health departments, through socioeconomic policies aimed at diminishing the risks of diseases, in a hierarchical flow.[11]

Hence, Brazilian states have adopted policies consisting of preventive strategies against congenital toxoplasmosis, with protocols for diagnosis, attendance and treatment among mothers and children, at public healthcare services.[12] These strategies have been established and validated in the state of Paraná and are available online under the name "*Mãe Paranaense*" ("Paraná-born Mothers").

In the northwestern part of the state of São Paulo, professionals responsible for prenatal healthcare among pregnant women are instructed to follow the primer of the Brazilian Ministry of Health. This primer provides guidelines for three serological investigations of anti-*T. gondii* antibodies among pregnant women living in regions of high endemicity. However, the lack of studies to certify situations of high endemicity of congenital toxoplasmosis may corroborate the perception that negligence in disease notification has been occurring. Although gestational and congenital toxoplasmosis were included through Ordinance no. 204, of February 17, 2016, among compulsory-notification diseases for which weekly reports and standardized guidelines and recommendations are required, some states have not registered any cases yet.

Hence, to improve the detection of gestational toxoplasmosis cases and to reduce occurrences of congenital toxoplasmosis, researchers and postgraduate students at a public university in the state of São Paulo proposed the implementation of a healthcare surveillance program for congenital toxoplasmosis in the northwestern region of the state of São Paulo, to be established in six steps in accordance with the *Mãe Paranaense* guidelines.[13,14]

OBJECTIVE

Through this study, we aimed to describe the aspects of prenatal care strategies in 13 municipalities within the regional healthcare unit of Araçatuba, in the northwestern region of the state of São Paulo in 2017. We focused on congenital toxoplasmosis and ascertained the possibility of implementing a surveillance program for congenital toxoplasmosis in this regional healthcare unit.

METHODS

In the state of São Paulo, according to Decree DOE no. 51,433, of December 28, 2006, healthcare is distributed into 17 Regional Health Departments (Departamentos Regionais de Saúde, DRS), which are responsible for coordinating the activities of the State Health Department with the municipalities and civil society, in order to promote better quality of life for the population of its coverage area. The region of Araçatuba is included in DRS II, which is composed of 40 municipalities covering about 724,570 inhabitants. These municipalities are grouped into three regional management board groups, namely: "Central," "dos Lagos," and "dos Consórcios".

All municipal healthcare managers present at the board meetings of the Regional Inter-Agency Committee (Comissão Intergestora Regional, CIR) were invited to participate in the project, which had the aim of improving the healthcare provided for pregnant women with congenital toxoplasmosis, through academic-scientific partnerships between epidemiological surveillance bodies and municipal health departments.

Among the municipal managers who agreed to participate, some information was requested through a questionnaire that was sent out via e-mail to each municipal health department. The data recorded were grouped in terms of the following general characteristics: infrastructure available in the municipalities for prenatal care and for making the serological diagnosis; the time at which trimestral screening was performed and the parameters adopted for this; and the confirmatory test and the place and circumstances used for notification of the infection (**Table 1**); and also according to the drug intervention (**Table 2**).

Information from each municipality was described individually and differences between strategies were recorded.

The manual "Gestational and congenital toxoplasmosis: health surveillance, diagnosis, treatment and conduct", which was created in the city of Londrina, Paraná, in 2006, was used as reference material. This material was then implemented in the state of Paraná as part of the program "Paraná-born Mothers – Books for healthcare provided for combating prenatal toxoplasmosis".[15]

The study "Implementation of the healthcare surveillance program for congenital toxoplasmosis in the northwestern region of the state of São Paulo" was approved by the local research ethics committee on April 27, 2018 (opinion report no. 2,625,140).

RESULTS

Out of the 40 municipalities that form the regional healthcare unit of Araçatuba, 13 agreed to participate in this project. In 12/13 municipalities (92.30%) that were surveyed, prenatal care is carried out in outpatient clinics at primary healthcare units. Between 17 and 110 prenatal medical appointments take place at each unit per month. In those with more than 45 prenatal appointments

per month, the services of the teams of the Family Health Strategy (Estratégia Saúde da Família, ESF) or the Family Health Support Center (Núcleo de Apoio à Saúde da Família, NASF) are available in order to develop complementary actions to promote pregnant women's health. However, in 1/13 municipalities (7.7%), these teams are unavailable. In that municipality, healthcare for all the 200 pregnant women is concentrated at an institution that specializes in promoting women's healthcare.

Table 1. Description of general characteristics of the healthcare provided towards preventing congenital toxoplasmosis, as reported by the 13 municipal health departments of the Regional Health Department II, in 2017

Parameter	Municipality													Reference*
	1	2	3	4	5	6	7	8	9	10	11	12	13	
General characteristics														
Number of PHUs for prenatal care	18	2	10	2	1	1	1	1	1	1	9	1	1	§
Number of pregnant woman receiving healthcare	1890	46	1100	89	*	34	20	200	21	30	358	*	42	§
Presence of ESF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Veterinarians in the NASF	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Personal educational activities	Yes	No	No	No	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes
Monthly prenatal appointments	6	8	6	9	6-7	12	10-12	8-10	6-14	8	9	14	9-12	§
Minimum number of US per pregnancy	2	3	2	*	2	4	12	3	3	3	2	7	5	4
Medical team available at prenatal visits	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Gynecology
	No	No	No	No	No	No	No	No	No	No	No	No	No	Obstetrics
	No	No	No	No	No	No	No	No	No	No	No	No	No	Infectiology
	No	No	No	No	No	No	No	No	No	No	No	No	No	Pediatrics
Infrastructure	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	PHU
Diagnostics														
Number of laboratories	3	1	6	1	0[a]	2	*	1	1[a]	2	2	1	1	§
Blood sample collection at PHU	No	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No	§
Trimestral screening														
Was screening done every trimester?	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Trimesters	1, 2	1, 2	1, 3	1, 3	1, 3	1, 2	1, 2	1	1	1, 3	1, 2	1	3	1, 2, 3
Serological methods	Yes	No	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	CMIA
	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	No	MEIA
	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	ELFA
Quantified antibody titers	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Available
Confirmatory test														
Parameter used to confirm infection	No	Yes	Yes	Yes	No	No	-	Yes	No	Yes	Yes	Yes	Yes	IgG avidity test
	No	No	No	No	No	No	No	No	No	No	No	No	No	IgG+ IgM- until 16th GW
Local laboratory	Yes	No	Yes	Yes	No	Yes	-	-	No	Yes	Yes	Yes	Yes	§
Screening sample used for confirmation	Yes	Yes	Yes	No	-	-	-	No	-	Yes	No	No	Yes	Yes
Time taken to obtain the result		2	7	7	-	15	-	10	-	20	5	7	20	§
Serological tests on NB	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	In gestational infection
Notification														
Notification at PHU	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	At PHU
Circumstances for notification	No	No	No	No	No	No	No	No	No	No	No	No	No	IgG and IgM Seroconversion
	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Until the 16th GW: IgG+ IgM+ and Low IgG avidity.
	No	No	No	No	No	No	No	No	No	No	No	No	No	After 16th GW: IgG+ IgM+

*Reference according to the implementation described by Mitsuka-Breganó, Lopes-Mori and Navarro, 2010.[14]

PHU = primary healthcare unit; ESF = Family Health Strategy (from the Portuguese "Estratégia Saúde da Família"); NASF = Family Health Support Center (from the Portuguese Núcleo de Apoio à Saúde da Família); NB = newborn; US = ultrasound; GW = gestational week; CMIA = chemiluminescent microparticle immunoassay; MEIA = microparticle enzyme immunoassay; ELFA = enzyme-linked fluorescent assay.

Educational activities relating to toxoplasmosis for pregnant women are carried out in 8/13 municipalities (61.53%) as stated in the strategies of the "*Mãe Paranaense*" guidelines. In five of the municipalities, no such action is carried out. In the other three municipalities, preventive information on infection is given collectively to groups of pregnant women.

Blood samples are collected from the pregnant women attended in all the municipalities, either directly at laboratories or at the primary healthcare unit, for forwarding to the laboratory. These laboratories for investigating anti-*T. gondii* immunoglobulin (Ig)G and IgM antibodies are either in the municipality or in a nearby town. In 1/13 municipalities, blood from pregnant women is collected at a laboratory in a nearby municipality.

Surveillance for gestational toxoplasmosis is performed once in 4/13 municipalities (30.76%), and twice in the remainder of the localities. In 12/13 municipalities (92.30%), the healthcare strategy involves screening in the first semester.

The serological methods of chemiluminescent microparticle immunoassay (CMIA), microparticle enzyme immunoassay (MEIA) or enzyme-linked fluorescent assay (ELFA), with quantitative presentation of antibodies, are used in 7/13 municipalities (53.85%). In the others, i.e. 6/13 municipalities (46.15%), this information is not obtained.

The test for avidity of IgG is not performed in 4/13 municipalities (30.76%). IgM-positive blood samples are forwarded for performing the avidity test in neighboring towns. This strategy is feasible for most of the municipalities because the results become available within two days. However, in two municipalities, the reports may take between 10 to 15 days, even though there is a laboratory in each of these municipalities. In 3/10 municipalities (30.00%), a new blood sample is collected for the avidity test.

The number of prenatal appointments per pregnant women ranged between six and 14, with completion of 2 to 12 ultrasound scans per patient. Only in one municipality is this diagnostic imaging test not performed.

Investigation of the presence of anti-*T. gondii* antibodies in infants, as part of the daily work routine, is not recommended in 12/13 municipalities (92.30%). In one municipality, this test is not performed even when there is a confirmed case of gestational infection.

Classification of pregnant women at risk of congenital toxoplasmosis, based on the serological results, is not carried out in one municipality; and in two there was no answer regarding this question. Concerning the criteria used to make the notification, the answer was "after confirming the infection" in 9/13 municipalities, while there was no response from one and the answer from two was incomplete, since it was stated that notification was only performed in cases in which the pregnancy was not more than 16 weeks.

Therapeutic intervention was inadequate in all the municipalities. According to the responses, it was implemented "after medical prescription," "after serological result" or "as soon as possible" in 8/13 municipalities. In the others, it was done after waiting for the result from the avidity test. Spiramycin was reported to be the active substance of choice by 12/13 municipalities.

In only 2/13 municipalities, the pregnant woman is reevaluated, and the choice of therapy is guided according to the gestational week (GW). Although this conduct is in accordance with the "*Mãe Paranaense*" guidelines, there is no immediate availability of spiramycin for pregnant women in 6/13 municipalities. The time between blood collection and the beginning of the treatment was described as between 7 and 60 days.

Detailed information about each municipality is available in **Tables 1** and **2**.

Table 2. Description of drug interventions within the healthcare provided to pregnant women for preventing congenital toxoplasmosis, as reported by the 13 municipal health departments of the Regional Health Department II, in 2017

Information	Municipality													Reference*
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Circumstance for prescription	No	No	No	No	No	No	No	No	No	No	No	No	No	IgG e IgM seroconversion.
	No	No	No	No	No	No	No	No	No	No	No	No	No	IgM +
Medicine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes	Yes	Yes	Spiramycin
	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Folinic Acid
	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Sulfadiazine
	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Pyrimethamine
Drug intervention according to GW	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes	Yes
Immediate availability of IgG avidity test	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	No	Yes
Days elapsed from blood collection to administration of medicine	7	15	30	7	60	15	7-10	15-30	30-40	20-30	7	15	-	§

*Reference according to the implementation described by Mitsuka-Breganó, Lopes-Mori and Navarro, 2010.[14]

§Information not available regarding a reference; GW = gestational week; IgG = immunoglobulin G; IgM = immunoglobulin M.

DISCUSSION

The strategies to prevent gestational toxoplasmosis during the prenatal period in the 13 municipalities surveyed in this region are not standardized. Overall, aspects such as the diagnosis, reference outpatient clinics, notification, health education activities and the medicines and healthcare provided for infected children differ. These differences may hinder earlier detection of gestational infection by *T. gondii*.

Among the actions adopted by these 13 municipalities in the northwestern region of the state of São Paulo in order to avoid infection by *T. gondii* in pregnant women, we identified particular matters that differed from what is recommended in the reference material used in our study, i.e. "Gestational and congenital toxoplasmosis: health surveillance, diagnosis, treatment and conduct." These differences have the potential to undermine the implementation of the prevention program for congenital toxoplasmosis in this region.

These weaknesses allow us to suggest interventions to minimize possible failures when undertaking actions among pregnant women, individually, per municipality. The overall aspects of the preventive healthcare actions against congenital toxoplasmosis adopted by municipal governments for prenatal care through SUS can be individually searched, in order to conform with the structure provided and adapt the strategies to the available resources.[16]

Analyses on the general characteristics of the preventive healthcare actions against congenital toxoplasmosis (**Table 1**) showed that primary healthcare units or healthcare units specializing in women's health were the places for completion of prenatal care in the municipalities surveyed. This information was provided by the respondent healthcare managers of the 13 municipalities investigated, through the questionnaires.

Through the ESF and NASF teams, more professionals are available to promote healthcare among pregnant women. These teams are available in municipalities where more than 45 pregnant women are attended per month. They were created in Brazil to reorganize primary healthcare, with interprofessional healthcare teams working in an integrated manner. Through this, the capacity for analysis and intervention concerning health problems and needs within the area of coverage is increased, in clinical, sanitary and environmental terms.[17] Thus, if toxoplasmosis is addressed by different professionals, knowledge about the disease is corroborated, which may increase the chances that it will be recognized in pregnant women in recognizing and that the risks of infection can be avoided.

The presence of members of the community in these teams, such as community health agents (agentes comunitários de saúde, ACS), facilitates creation of bonds with the population and interactions with the team of healthcare professionals.[18] Thus, indirectly, this assists in health education and in actively seeking out pregnant women to ensure that they receive complete prenatal follow-up. Incorporation of veterinarians and graduates in epidemiology, public health, zoonoses and food inspection, among others, in NASF teams is highly recommended, in order to add quality to the dissemination of knowledge to the population. Successful work by veterinarians has been reported in relation both to prevention of zoonoses[19,20] and to responsible conduct towards companion animals.[19] It is paramount that women understand the *T. gondii* cycle and its transmission routes, in order to avoid infection during pregnancy.[21]

In the states of Rio de Janeiro and Paraná, lack of knowledge about toxoplasmosis was observed among, respectively, 232/405 (57.28%) and 177/330 (53.63%) pregnant women attended through the municipal public healthcare network.[22] In a city in the northwestern region of the state of São Paulo, an investigation on the degree of knowledge about toxoplasmosis and leishmaniasis among 123 residents showed that 29/123 (57.0%) of the respondents did not recognize the term "zoonosis," 68/123 (55.3%) did not know how to prevent toxoplasmosis and, although 119/123 (96.7%) stated that they knew what leishmaniasis was, dogs were deemed to be transmitters of infection through their feces, urine, bites or licking, or believed that transmission occurred through animal blood, mosquito bite or the mosquitos' contaminated feces mosquitos.[23] This result confirmed that there is a need for dissemination of knowledge about the *T. gondii* cycle, concerning the disease transmission route and symptoms and the damage caused to fetuses, in order to intensify the strategy of prevention of gestational infection.

Health education for pregnant women should be conducted on a one-to-one basis, to achieve better results. This was seen among pregnant women in a municipality in Paraná, Brazil, who reported that they gained knowledge of toxoplasmosis through lectures (120/153; 78.4%), group reading (24/153; 15.7%) and pamphlets (15/153; 9.8%). Better knowledge of preventive strategies against congenital and gestational toxoplasmosis has been correlated with health professionals' participation in an integrated network.[21]

Early diagnosis is crucial for preventing congenital infection. Some aspects of how laboratory tests are organized, such as daily test production capacity and the sample collection site, can reduce the time taken to detect acute infection.

There is a lack of specific guidance from the Brazilian Ministry of Health regarding the place at which blood collection should be performed, for investigating the presence of anti-*T. gondii* antibodies. Nonetheless, shortening the time taken to implement therapeutic intervention after pregnant women become infected is crucial for reducing the damage to fetuses.[24] In the state of Minas Gerais, Brazil, all blood samples from pregnant women are collected on filter paper and are sent to the reference laboratory within 24 hours, using a specialist postal service for transporting this material. The result is made available online, with consequent release of the therapeutic drug

through SUS, if necessary. This highly organized system in Minas Gerais shows that, regardless of the place at which blood samples are collected, efforts should be concentrated on implementation of a flow process for transportation of samples, so as to optimize the time that elapses between blood collection and drug interaction.

Diagnostic screening for gestational toxoplasmosis, which is recommended at the beginning of each gestational trimester, was the matter of greatest divergence from the guidelines. This was not incorporated within the healthcare strategy of any of the municipalities in our research.

Infections in the last trimester cause mental disorders and hearing impairments that are often manifested after birth.[25,26] This late diagnosis may be related to negligent evaluation in the third trimester. However, since the rate of vertical transmission of *T. gondii* increases with increasing gestational age, trimestral serological evaluation, at least, is essential within surveillance programs for congenital toxoplasmosis.[9] Clinical patterns of asymptomatic acute infection, which may occur at any stage of pregnancy, can only be demonstrated through serological monitoring. Detection of these cases increases the chances that the baby will grow without after-effects, since it triggers a flow of actions for early and continuing treatment during pregnancy and after birth. Moreover, the costs of treatment of the disease due to infection at the end of pregnancy may be higher than the costs of serological monitoring within prenatal care. Such situations may have an impact on a country's economy. This was seen in Austria, where the government was able to save 258 million euros over a 17-year period through bimonthly serological evaluations on pregnant women. These evaluations reduced the extent of damage caused by congenital toxoplasmosis.[10]

The diagnostic methodology needs to include quantification of antibodies in order to aggregate information that can guide the medical conduct until acute infection has been confirmed through laboratory data. By making this quantitative information available, antibody curves for paired samples over 15-day intervals can be determined. This aids in interpreting the results from IgM-reactive individuals. Another way to confirm infection is to use an IgG avidity test on samples that were positive for IgM in screening tests.[14]

To make this diagnosis, it is essential to define a flowchart for confirming recent infections. IgG avidity tests should be requested within the first 16 weeks of pregnancy, if the pregnant woman is positive for IgG and IgM in the screening test. To achieve this, urgency in temporal dynamics between conducting tests on samples and beginning the treatment for congenital toxoplasmosis is required. Thus, we suggest that in the cases of the two municipalities, in which the reports are received only 20 days after the samples were collected, alternatives need be discussed with the aim of shortening these temporal dynamics. The healthcare managers responsible for prenatal care should advise the laboratory service to perform the avidity confirmatory test on the same sample as used for screening.

In this proposal for a program for preventing toxoplasmosis, efforts need to be made to facilitate drug interventions in urgent cases of gestational toxoplasmosis. To do so, it is paramount to define a strategic flowchart with diagnostic actions that go from taking samples from pregnant women to production of the diagnostic report that is to be given to the doctor responsible for the prenatal care.[13]

Prenatal care in the municipalities surveyed was unsatisfactory. Moreover, there was a need to change the number of ultrasounds performed, in order to achieve bimonthly monitoring, and monthly monitoring in cases in which changes to the fetus are observed. Through ultrasounds, conditions such as ventriculomegaly, higher hepatosplenic or periventricular density, focal injuries to the brain tissue, calcification, punctate lesions, fetal ascites or greater placental thickness can be ascertained.[27]

In Brazil, compulsory notification for gestational toxoplasmosis has only been established in sentinel units. These units are used in Brazil to improve the notification of diseases without any use of a specific questionnaire for epidemiological investigation. Thus, it might be possible to aim towards a better notification service for acute toxoplasmosis if no sentinel units are available.

Classification of the risk of congenital toxoplasmosis and the criteria for notification need to be intensified. This is especially important after two-thirds of pregnancy has passed. This is the point at which the greatest lack of monitoring has been reported. This lack of monitoring may be due either to lack of prenatal follow-up on the part of pregnant women, or to lack of requests for serological tests at this time, which was reported in several municipalities. The recommendation given in the program is that detection of IgG and IgM-reactive samples with low IgG avidity should be notified until the 16th gestational week, and that seroconversion of IgG and IgM when IgG and IgM are reactive should be notified at any time during prenatal care.[15]

The level or quality of therapeutic intervention reflects the success of newborn recovery and damage reduction.[14] In 84.6% of the municipalities, the quality of therapeutic intervention was insufficient, especially regarding the adequacy of active substances that were administered after confirmation of acute gestational toxoplasmosis, but also concerning immediate availability of spiramycin and the time between blood collection and the beginning of the treatment.

Use of spiramycin in gestational toxoplasmosis protects the fetus from ocular damage, as observed in a cohort study conducted in Colombia. In that study, ocular toxoplasmosis was found in 1/15 children (6.6%) from pregnant women who used spiramycin, whereas it was found in 5/8 babies (62.5%) from untreated pregnant women, and in two of these cases, involvement of the central nervous system was verified.[28]

In a cohort study conducted in Goiânia (GO), Brazil, congenital infection was detected in 58.33% of newborn babies from pregnant women who received treatment with spiramycin, and in 18.6% of them the damage was severe. On the other hand, among untreated pregnant women, infection was found in 73.04% of their babies, with severe damage to health in 60.7% of them.[4]

In treating gestational toxoplasmosis to avoid congenital toxoplasmosis spiramycin needs to be added. This acts as a parasitostatic agent on the placental barrier. Sulfadiazine and pyrimethamine antiparasitics are added to act on fetal tissues. Folinic acid needs to be administered whenever its antagonist, pyrimethamine, is activated.[15]

Through the instrument used, we were able to see that actions conflicting with the strategy proposed were occurring in all the participating municipalities at this step of implementation, regarding all aspects evaluated. The healthcare strategies seen in all the municipalities investigated in our study presented at least one aspect that diverged from what is described in the program "Paraná-born Mothers – Books for healthcare provided for combating prenatal toxoplasmosis".

The profile of preventive healthcare actions, screening and confirmatory diagnoses, prenatal care, healthcare provision for newborns, notifications and drug interactions can guide the actions for the next stage of implementation of the healthcare surveillance program for congenital toxoplasmosis in the northwestern region of the state of São Paulo.

CONCLUSION

It needs to be acknowledged that the methodology used in the present study, i.e. interpretation of data collected via email, may have led to some bias. However, to the best of the authors' knowledge, no guidelines on how to start a preventive program for gestational and congenital toxoplasmosis currently exist. Therefore, the simple investigative methodology presented here can be used in other locations as the first stage in implementing a preventive program for combating gestational and congenital toxoplasmosis.

We observed differences in the prenatal strategies among the municipalities surveyed. However, the differences in strategies that were detected confirm that there is a need to implement a healthcare surveillance program for congenital toxoplasmosis.

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Address for correspondence:
Katia Denise Saraiva Bresciani
R. Clóvis Pestana, 793
Dona Amélia — Araçatuba (SP) — Brasil
CEP 16050-680
Tel. (+55 18) 3636-1370
E-mail: katia.bresciani@unesp.br

Satisfaction with body weight among adolescents with excess weight: findings from a cross-sectional population-based study

Mariana Contiero San Martini[I], Daniela de Assumpção[II], Marilisa Berti de Azevedo Barros[III], Antonio de Azevedo Barros Filho[IV], Josiemer Mattei[V]

Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil

[I]PhD. Nutritionist, Department of Pediatrics, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
orcid.org/0000-0002-0160-5576

[II]PhD. Nutritionist, Department of Pediatrics, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
orcid.org/0000-0003-1813-996X

[III]MD, PhD. Titular Professor, Department of Public Health, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
orcid.org/0000-0003-3974-195X

[IV]MD, PhD. Collaborating Associate Professor, Department of Pediatrics, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
orcid.org/0000-0001-6239-1121

[V]MPH, PhD. Associate Professor, Department of Nutrition, Harvard T. H. Chan School of Public Health, Harvard University, Boston (MA), United States.
orcid.org/0000-0001-5424-8245

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ABSTRACT

BACKGROUND: Individuals who are overweight or obese often underestimate their size, and they are less likely to consider their weight status to be a health problem and consequently to make lifestyle changes.

OBJECTIVES: To estimate the proportion of satisfaction with weight among adolescents classified as overweight/obese, according to sociodemographic factors, morbidities and health-related behaviors.

DESIGN AND SETTING: Cross-sectional population-based study conducted among adolescents aged 10 to 19 years in the city of Campinas (SP), Brazil.

METHODS: The sample (n = 217) included participants with self-reported weight and height who were classified as overweight or obese, based on body mass index (BMI) according to age-specific cutoff points recommended by the World Health Organization. Participants whose answer to the question: "Would you like to gain or lose weight?" was "no" (i.e. no change) were deemed to be satisfied with their body weight. Odds ratios and 95% confidence intervals (95% CI) were calculated using logistic regression.

RESULTS: The proportions of the respondents who were satisfied with their weight were 75.8% (95% CI: 65.3-83.9) among the overweight adolescents and 24.2% (95% CI: 16.1-34.7) among the obese adolescents (P < 0.01). Satisfaction was lower among individuals aged 15 to 19 years (versus 10 to 14 years), those born outside of Campinas (versus in Campinas), those with ≥ 8 household appliances (versus < 8), and those reporting ≥ two health complaints (versus none).

CONCLUSIONS: More than half of the overweight adolescents and almost a quarter of the obese adolescents were satisfied with their weight. These results support the need for strategies for healthy weight management among Brazilian adolescents.

INTRODUCTION

The prevalence of obesity among children is 5.0% (107.7 million) and 12.0% among adults (603.7 million), according to a study conducted in 195 countries. Between 1990 and 2015, most nations experienced continuous increases in prevalence.[1] In 2010, overweight and obesity were estimated to contribute 3.4 million deaths, 3.8% of disability-adjusted life-years and 3.9% of years of life lost among adults worldwide.[2]

In Brazil, the projections of overweight and obesity are of particular concern. In the adult population (≥ 18 years), the prevalence of overweight increased from 30.9% to 33.2% and obesity from 11.9% to 17.5%, from 2006 to 2013, which reflected an average annual increases of 2.3% and 5.6% in the respective prevalences.[3] Among Brazilian adolescents aged 10 to 19 years, in 2008/2009, 20.5% were classified as overweight and 4.9% as obese.[4] A study on adolescents aged 13 to 17 years found that 23.7% and 7.8% were classified as overweight and obese, respectively, in 2015.[5] In addition, it has been estimated that by 2022, 13.8% of boys and 7.8% of girls in Brazil will be classified as obese.[6]

The Brazilian government has continuously monitored the trends of overweight and obesity and has developed strategies to reduce the increasing prevalence, such as encouraging breastfeeding, promoting physical activity, supplying healthy foods in the school environment, regulating food advertising aimed at children and adolescents and restricting the marketing of food products high in salt, sugar and unhealthy fats.[6] Given the reported increases in obesity among

Brazilians, these government-sponsored strategies are possibly not having much effect with regard to reducing excess weight in the population.

It is common for adolescents to have distorted body perceptions.[7] They experience multiple physical, emotional and sociocultural influences that can affect self-perception of body image, thus causing dissatisfaction and even a distorted view of the body's own shape.[8] According to the National School Health Survey (PeNSE 2015), approximately 20.0% of adolescents (13 to 17 years old) perceived themselves to be fat or very fat.[5] Another study revealed that 13.5% of boys who were overweight or obese wanted to gain weight, probably with the expectation of gaining muscle mass. Among girls, there was greater dissatisfaction with overweight and obesity.[9]

Individuals who are overweight or obese tend to distort their weight perception, often through underestimating the size of certain body parts. They are less likely to consider their weight status to be a health problem and consequently to make lifestyle changes.[7,10] Additionally, distorted body perceptions are more often present among people who experienced gain of weight later in life than among those that have been obese since childhood.[7] Studies that evaluate weight satisfaction among adolescents who are overweight/obese are rare, and it is important to identify the epidemiological profile of this group in order to develop health promotion actions.

OBJECTIVE

The objective of this study was to estimate the proportion of satisfaction with weight among adolescents classified as overweight or obese according to sociodemographic factors, morbidities and health-related behaviors.

METHODS

Study population

Data from a cross-sectional population-based health survey known as ISACamp were used. In this survey, information from non-institutionalized individuals residing in the urban area of Campinas, Brazil, were collected. This area has a population of more than one million inhabitants, living within 100 kilometers from the state capital of São Paulo, Brazil. The data were collected from February 2008 to April 2009.

The sample of the survey was recruited by means of probabilistic sampling procedures, using cluster sampling, in two stages: census tract and household. In the first stage, 50 census tracts were drawn, with probability proportional to the number of households. The census tracts of the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE) were used, based on the 2000 census. The households of the selected census tracts were visited to obtain an up-to-date list of addresses, considering the length of time that had elapsed since the last census (which was in the year 2000). In the second stage, households were randomly selected.

The survey population consisted of three age domains: adolescents (10 to 19 years), adults (20 to 59 years) and elderly people (60 years or over). Only adolescents were analyzed in this study. The sample size was 1,000 people in each age domain, considering the following: maximum variability for the frequency of the events studied (P = 0.50); 95% confidence intervals (z = 1.96); sampling error between 4% and 5%; and design effect equal to 2. The response rate was taken to be 80% and, therefore, the sample size was corrected to 1,250. To achieve the desired sample size, 2,150, 700 and 3,900 households were drawn for interviews with adolescents, adults and elderly people, respectively.

Data were collected through a survey structured into 14 thematic blocks, which had been tested in a pilot study. The survey was applied by trained and supervised interviewers. The thematic block on food habits contained questions regarding weight and height (self-reported), practices used for weight loss and frequency of food consumption.

This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Research Ethics Committee of Universidade Estadual de Campinas (UNICAMP) on January 13, 2015 under protocol number 931.774. Written informed consent was obtained from all subjects.

Study variables

Satisfaction with body weight was the dependent variable and was assessed through the question "*Would you like to gain or lose weight*?", with three answer options: "no" (i.e. no change); "yes, I'd like to lose weight"; and "yes, I'd like to gain weight". If the participants answered "yes" to this question, they were then asked how much they would like to weigh. If they wanted to lose weight, they were asked whether they were undertaking any practices to lose weight, and if so, this was probed using a list of practices.

The independent variables that were assessed included demographic and socioeconomic characteristics, health-related behaviors and morbidities.

The sociodemographic characteristics selected were sex, adolescent age group (categorized as 10-14 years versus 15-19 years), place of birth (Campinas versus other city/state), *per capita* household income (in monthly minimum wages), education level of household head (in years of schooling), number of appliances in the household (out of a total of 15 items) and having health insurance (yes or no).

Health-related behaviors included food consumption, weight loss practices and physical activity. The participants' weekly consumption of fruits, vegetables and soft drinks was assessed from

a simple food frequency questionnaire, in which the following responses were possible: "every day"; "four to six days a week"; "one to three days a week"; "less than once a week"; or "less than once a month". These were then grouped into "≥ 4 times a week" versus "< 4 times a week". The respondents were asked whether they did any practices to lose weight (yes or no), and if so, what practices were followed, from among these options: "careful about food intake"; "diet"; or "exercise, sports or walking". Their leisure physical activity practices were investigated. Adolescents aged 10-17 years who practiced at least 60 minutes of physical activity per day, at least five days a week, were classified as "active". Adolescents aged 18-19 years who performed at least 150 minutes per week, for three days, were also classified as "active". These age classifications for physical activity levels followed the definitions of the World Health Organization. Adolescents who practiced physical activity at lower levels than recommended were classified as "insufficiently active". Those who did not do any kind of physical activity were classified as "inactive".[11]

The participants were asked to self-report any chronic diseases that had been diagnosed by a physician or other health professional. These could include hypertension, diabetes, cancer, arthritis, osteoporosis, asthma, heart disease, cancer, tendonitis and circulation problems. Likewise, they were asked about any health complaints such as headache/migraine, allergy, emotional problems, dizziness/vertigo, insomnia and back pain.

Nutritional status was evaluated using body mass index (BMI), defined as weight (kg)/height^2 (m). This was calculated from self-reported weight and height and was classified according to World Health Organization age-specific BMI cutoff points: underweight BMI < 3rd percentile; normal weight BMI ≥ 3rd percentile and ≤ 85th percentile; overweight BMI > 85th percentile and ≤ 97th percentile; and obese BMI > 97th percentile.[12]

Statistical analysis

This analysis only included adolescents aged 10 to 19 years of both sexes with self-reported weight and height and who were classified as overweight or obese. Among the selected households in which adolescents were present, 14.8% were not included because the resident was absent or refused to provide information. Out of the 955 adolescents identified from the households that had been drawn, 31 refused to participate. Self-reported weight and height data were collected in relation to 820 individuals. Among these, 217 were classified as overweight (16.2%) or obese (10.2%) and were included in this analysis.

The proportion of the adolescents who were satisfied with their body weight according to the independent variables was estimated. Differences according to categories were tested using Pearson's chi-square test, considering a significance level of 5%. Odds ratios and 95% confidence intervals (95% CI) were calculated using logistic regression. The sociodemographic and morbidity variables with P < 0.20 in the bivariate analysis were added to the model and those that continued to present P < 0.05 were kept in the final model.

The interview data were entered into a database that had been prepared in the EpiData 3.1 software (EpiData Association, Odense, Denmark). The statistical analyses were done in the Stata 11.0 software (Stata Corp., College Station, USA), in the survey module, which allows analysis of complex sample data.

RESULTS

Body weight satisfaction was higher among younger adolescents aged 10 to 14 years (84.3%), individuals who reported not having any chronic disease (91.3%), those without health complaints (53.1%) and those classified as overweight (75.8%). Greater desire to lose weight was noted among adolescents who had ≥ 8 appliances in their home (57.3% among those with 8-15 appliances and 33.9% among those with 16 or more), compared with those with < 8 appliances (8.8%) (P < 0.01) (**Table 1**).

Trying to lose weight was significantly associated with weight satisfaction/dissatisfaction (P < 0.01), such that more dissatisfied adolescents reported trying to lose weight. More than half of the dissatisfied adolescents (56.0%) practiced physical activity, almost a quarter were dieting (22.9%) and more than 60% reported eating raw vegetables more frequently (**Table 2**).

Lower odds regarding satisfaction with excess weight were found among older adolescents (15 to 19 years old), participants born in another town or state, those in the segments that had the highest *per capita* household income (≥ 1.5 monthly minimum wages), those with higher numbers of appliances in the household (eight or more), those who reported having one or more chronic diseases and those who reported having two or more health problems (**Table 3**).

The final logistic regression model showed lower satisfaction with weight among adolescents aged 15 to 19 years old, participants who were born outside Campinas, those who had more appliances in the household and those who mentioned having two or more health complaints (**Table 4**).

DISCUSSION

The present study found that 75.8% of the adolescents who were overweight and 24.2% who were obese were satisfied with their weight. Mäkinen et al.[13] reported that 27.5% of their sample of adolescents presenting overweight/obesity were satisfied with their weight. Among these adolescents, 20.5% were girls (versus 79.5% who felt that they had excess weight) and 32.4% were boys (versus 66.6% who felt that they had excess weight and 1.0% who felt that they were underweight).

It was observed in the present study that younger adolescents were more satisfied with their weight. This was concordant with

other studies in which teenagers with diverse weight status were evaluated.[14,15] Concern about weight begins at the transition from adolescence to adulthood. This may be an appropriate stage for interventions focusing on health promotion and healthy eating.[5] A qualitative study conducted among adolescents between 11 and 15 years of age who were classified as overweight or obese found that concern about weight or desire to lose weight began in the later phase of adolescence, when these individuals started to follow physical activity and dieting as strategies for weight control.[16] Older adolescents tend to recognize that taking care of weight is a personal responsibility, implemented through making food choices and doing physical activity, especially at the time of acquiring autonomy and independence from parents.[16]

Being satisfied with body weight can prevent weight gain and binge eating. Ricciardelli et al.[17] evaluated a group of girls for 11 years and observed that the young women who were satisfied with their bodies were 85% less likely to develop binge eating compared to those who were less satisfied.[17] A study conducted in Minneapolis, United States, followed 376 girls who were classified as overweight or obese for five years and found that these was an association between body satisfaction and lower weight gain.[18]

In our data, females showed higher weight dissatisfaction than males: 64.1% versus 35.9%, although this difference was not statistically significant. This result agrees with the findings from a report on adolescents in the 9th grade of elementary school that showed that there was twice as much body dissatisfaction (23.3%)

Table 1. Proportions of satisfaction/dissatisfaction with weight among adolescents aged 10 to 19 years who were overweight or obese, according to sociodemographic and morbidity factors and nutritional status. ISACamp health survey, 2008/2009

	n	% (95% CI)			P-value*
		Satisfied	Wished to gain weight	Wished to lose weight	
Sex					
Male	127	64.1 (54.7-72.5)	72.4 (20.0-96.5)	55.4 (45.4-64.9)	0.34
Female	90	35.9 (27.5-45.3)	27.6 (3.5-80.0)	44.6 (35.1-54.6)	
Age (years)					
10 to 14	147	84.3 (74.3-90.9)	75.9 (23.0-97.1)	57.5 (48.2-66.2)	**< 0.01**
15 to 19	70	15.7 (9.1-25.7)	24.1 (2.9-76.9)	42.5 (33.7-51.7)	
Place of birth					
Campinas	173	87.7 (76.2-94.1)	75.9 (23.0-97.1)	74.7 (61.9-84.2)	0.09
Other town/state	44	12.3 (5.9-23.8)	24.1 (2.9-76.9)	25.3 (15.8-38.1)	
***Per capita* income (monthly minimum wages)**					
< 0.5	58	32.5 (22.8-44.0)	24.1 (2.9-76.9)	23.0 (15.8-32.1)	
≥ 0.5 to < 1.5	111	52.4 (41.9-62.7)	24.1 (2.9-76.9)	50.2 (38.3-62.0)	0.15
≥ 1.5	48	15.0 (7.9-26.7)	51.7 (12.3-89.1)	26.8 (18.1-37.9)	
Schooling of head of household (years)					
0 to 7	79	32.7 (19.2-49.8)	24.1 (2.9-76.9)	38.4 (28.0-50.0)	0.66
8 or more	136	67.3 (50.2-80.8)	75.9 (23.0-97.1)	61.6 (50.0-72.0)	
Number of appliances in the home					
0 to 7	42	35.8 (21.6-53.0)	0.0	8.8 (3.8-19.2)	
8 to 15	115	45.2 (31.4-59.7)	48.3 (10.8-87.7)	57.3 (47.4-66.6)	**< 0.01**
16 or more	60	19.0 (9.6-34.1)	51.7 (12.3-89.1)	33.9 (23.5-46.1)	
Health insurance					
Yes	77	28.9 (18.7-41.9)	24.1 (2.9-76.9)	42.7 (28.3-58.3)	0.18
No	137	71.1 (58.1-81.3)	75.9 (23.0-97.1)	57.3 (41.6-71.7)	
Number of chronic diseases					
0	175	91.3 (81.4-96.2)	75.9 (23.0-97.1)	75.7 (67.0-82.7)	**0.02**
1 or more	39	8.7 (3.8-18.6)	24.1 (2.9-77.0)	24.3 (17.3-33.0)	
Number of health complaints					
0	89	53.1 (40.3-65.5)	0.0	34.5 (27.0-42.8)	
1	61	37.0 (27.7-47.5)	75.9 (23.0-97.1)	21.3 (14.8-29.7)	**< 0.01**
2 or more	67	9.8 (4.8-19.0)	24.1 (2.9-76.9)	44.2 (35.3-53.5)	
BMI (kg/m²)					
Overweight	133	75.8 (65.3-83.9)	100.0**	51.5 (43.8-59.1)	**< 0.01**
Obesity	84	24.2 (16.1-34.7)	0.0	48.5 (40.9-56.2)	

n = number of individuals in the unweighted sample; 95% CI = 95% confidence interval; BMI = body mass index.
*P-value from chi-square test; **four overweight adolescents reported that they wished to gain weight.

among girls than among boys (11.6%), thus suggesting that girls were more likely to feel that they had excess weight and that boys had a greater desire to acquire a strong and muscular body.[5]

Social norms tend to value a slim body as an ideal for girls and well-defined musculature as an ideal for boys. However, this is unrealistic and unreachable for most people.[19,20] The media and social networks disseminate the idea that slim women and muscular men represent a benchmark for success, competence and sexual attraction.[21] On the other hand, people who are considered to be overweight or obese are usually stereotyped as lazy and careless with their own health.[22]

Lower body satisfaction can lead to adoption of unhealthy behaviors[19] and to negative evaluation of health status.[23] This was noted in our study, since individuals who had two or more health complaints had lower body weight satisfaction. It is likely that reverse causation may be operating.

In this study, we found that the majority of both satisfied and dissatisfied adolescents practiced some level of physical activity within the context of leisure. However, only dissatisfied adolescents did something to lose weight, which in most cases consisted of exercising. On the other hand, in a prospective study on individuals aged 9 to 14 years who were overweight or obese, the opposite was found, i.e. many of them did not practice exercise but, instead, did dieting for weight control and nonetheless gained weight.[24] Another study showed that adolescents who were overweight, compared with those of healthy weight, presented higher prevalences of physical inactivity, eating disorders and health self-assessed as fair or poor; and lower prevalence of dating.[14]

Another study, also conducted in the United States, revealed that adolescents from 11 to 17 years old with higher purchasing power were more dissatisfied with weight.[25] Similar data were found in the present study, through considering the number of household appliances to be a proxy for income.

One limitation of this study was its use of a single-item question to assess satisfaction with body weight, instead of a scale. This study had a cross-sectional design that provided a small-sized sample of adolescents who were classified as overweight or obese, through use of self-reported weight and height measurements. The results from validation studies on weight and height have shown that these measurements are influenced by the sociodemographic and behavioral characteristics of the age group evaluated.[26,27] Individuals with excess weight, adolescents and females tend to underestimate weight. Furthermore, people of short stature, females and teenagers tend to overestimate height. These situations leads to errors of classification of both weight and height status.[28,29] On the other hand, one study conducted in the city of São Paulo (which is near the city of Campinas) found that self-reported measurements showed good validity in relation to measurements that were made.[30] We analyzed data that had been collected in 2008-2009 and which formed part of a population-based health survey

Table 2. Proportions of satisfaction/dissatisfaction with weight among adolescents aged 10 to 19 years who were overweight/obese, according to health-related behaviors. ISACamp health survey, 2008/2009

Variables	n	% (95% CI)		P-value*
		Satisfied	Dissatisfied	
Leisure physical activity				
Active	50	15.9 (8.4-28.0)	27.2 (19.6-36.6)	
Insufficiently active	105	58.0 (41.8-72.6)	43.4 (35.4-51.8)	0.14
Inactive	62	26.1 (14.7-41.9)	29.3 (21.7-38.4)	
Fruit consumption (weekly frequency)				
≥ 4 times	111	58.4 (44.9-70.9)	47.0 (36.9-57.3)	0.17
< 4 times	106	41.5 (29.1-55.1)	53.0 (42.7-63.1)	
Raw vegetable consumption (weekly frequency)				
≥ 4 times	125	53.5 (42.7-64.0)	60.3 (51.6-68.5)	0.97
< 4 times	92	46.5 (36.0-57.3)	39.7 (31.5-48.4)	
Soft drink consumption (weekly frequency)				
≥ 4 times	95	49.7 (35.7-63.7)	40.3 (32.4-48.8)	0.20
< 4 times	122	50.3 (36.3-64.3)	59.7 (51.2-67.6)	
Do you do anything to lose weight?				
Yes	53	0.0	39.7 (31.9-48.1)	**< 0.01**
No	164	100.0**	60.3 (51.9-68.1)	
What are you doing?				
Dieting	12	0.0	22.9 (13.7-35.7)	a
Exercise/sport/walking	30	0.0	56.0 (41.8-69.2)	

n = number of individuals in the unweighted sample; 95% CI = 95% confidence interval; % = percentage.

*P-value from chi-square test; **82 adolescents who were satisfied with their excess weight reported that they were not doing anything to lose weight; [a]It was not possible to calculate the p-value because none of the satisfied adolescents were doing dieting and/or physical activity.

and that is undertaken periodically, which allows monitoring of body weight satisfaction among adolescents.

Hardly any studies[13,14,18] have evaluated weight satisfaction among adolescents who are overweight or obese. Hence, more are needed, in order to make important contributions towards combating this growing epidemic and improving the quality of life of this population. Measures need to be taken in order to address the duality that exists between young people who are not concerned about their weight, and therefore do not take healthy actions and may develop future health problems, and those who are overly worried about their weight and take inappropriate measures or develop eating disorders.

CONCLUSION

This study aimed to depict the extent of satisfaction with weight among a representative sample of adolescents in a large Brazilian city. We found that more than half of these adolescents who were overweight and almost a quarter of those who were obese were satisfied with their weight. None of the adolescents who were satisfied with regard to their excess weight were following any practices aimed towards losing weight. A lower likelihood of satisfaction with body weight was noted among older adolescents (15 to 19 years), adolescents who were natives of other towns or states, those of higher socioeconomic level and those who mentioned more health complaints. These results

Table 3. Proportions of satisfaction with weight among adolescents who were overweight or obese, according to sociodemographic factors and morbidities. ISACamp health survey 2008/2009

Variables	n	Satisfied % (95% CI)	P-value*	OR (95% CI)
Sex				
Male	127	64.1 (54.7-72.5)	0.15	1
Female	90	35.9 (27.5-45.3)		0.7 (0.4-1.1)
Age (years)				
10 to 14	147	84.3 (74.3-90.9)	**< 0.01**	1
15 to 19	70	15.7 (9.1-25.7)		**0.2 (0.1-0.5)**
Place of birth				
Campinas	173	87.7 (76.2-94.1)	**0.03**	1
Other town/state	44	12.3 (5.9-23.8)		**0.4 (0.2-0.9)**
***Per capita* income (monthly minimum wages)**				
< 0.5	58	32.5 (22.8-44.0)		1
≥ 0.5 to < 1.5	111	52.4 (41.9-62.7)	0.08	0.7 (0.4-1.5)
≥ 1.5	48	15.0 (7.9-26.7)		**0.4 (0.2-0.9)**
Schooling of head of household (years)				
0 to 7	79	32.7 (19.2-49.8)	0.51	1
8 or more	136	67.3 (50.2-80.8)		1.3 (0.6-2.6)
Number of appliances in the home				
0 to 7	42	35.8 (21.6-53.0)		1
8 to 15	115	45.2 (31.4-59.7)	**< 0.01**	**0.2 (0.1-0.5)**
16 or more	60	19.0 (9.6-34.1)		**0.1 (0.04-0.4)**
Health insurance				
Yes	77	28.9 (18.7-41.9)	0.11	1
No	137	71.1 (58.1-81.3)		1.8 (0.9-3.7)
Number of chronic diseases				
0	175	91.3 (81.4-96.2)	**< 0.01**	1
1 or more	39	8.7 (3.8-18.6)		**0.3 (0.1-0.7)**
Number of health complaints				
0	89	53.1 (40.3-65.5)		1
1	61	37.0 (27.7-47.5)	**< 0.01**	1.0 (0.5-2.0)
2 or more	67	9.8 (4.8-19.0)		**0.1 (0.06-0.3)**

n = number of individuals in the unweighted sample; 95% CI = 95% confidence interval; OR = odds ratio; % = percentage.
*P-value from chi-square test.

Table 4. Final logistic regression model for satisfaction with weight among overweight/obese adolescents. ISACamp health survey 2008/2009

Variables	OR	95% CI	P-value*
Sex			
Male	1		
Female	0.71	0.4-1.3	0.24
Age (years)			
10 to 14	1		
15 to 19	0.21	0.1-0.5	**< 0.01**
Place of birth			
Campinas	1		
Other town/state	0.23	0.1-0.7	**0.01**
Number of appliances in the home			
0 to 7	1	1	
8 to 15	0.14	0.05-0.4	**< 0.01**
16 or more	0.10	0.03-0.3	**< 0.01**
Number of health complaints			
0	1	1	
1	1.18	0.5-2.8	0.71
2 or more	0.16	0.05-0.5	**< 0.01**

OR = odds ratio; 95% CI = 95% confidence interval; % = percentage.
*P-value from chi-square test, adjusted according to all variables in this table.

confirm that there is a need for strategies that would promote weight control and healthy lifestyle habits.

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Address for correspondence:
Mariana Contiero San Martini
R. Tessália Vieira de Camargo, 126
Cidade Universitária — Campinas (SP) — Brasil
CEP 13083-887
Tel. (+55 19) 3521-8978
E-mail: maricsm.02@gmail.com

Clinical simulation strategies for knowledge integration relating to initial critical recognition and management of COVID-19 for use within continuing education and health-related academia in Brazil: a descriptive study

Carolina Felipe Soares Brandão[I], Gabriela Furst Vaccarezza[II], João Carlos da Silva Bizario[III], Aécio Flavio Teixeira de Gois[IV]

Universidade Municipal de São Caetano do Sul (USCS), São Caetano do Sul (SP), Brazil

[I]BSc, MSc, PhD. Professor, Simulation Laboratory of the Medicine Program, Universidade Municipal de São Caetano do Sul (USCS), São Caetano do Sul (SP), Brazil.
orcid.org/0000-0002-7861-565X

[II]DDS, MSc. Professor of Medicine Program, Universidade Municipal de São Caetano do Sul (USCS), São Caetano do Sul (SP), Brazil.
orcid.org/0000-0002-2179-5338

[III]MD, MSc, PhD. Director of Medicine Program, Universidade Municipal de São Caetano do Sul (USCS), São Caetano do Sul (SP), Brazil.
orcid.org/0000-0002-2632-2476

[IV]MD, MSc, PhD. Cardiologist and Adjunct Professor, Disciplines of Emergency and Evidence-Based Medicine, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0003-0217-1463

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Patient safety.

ABSTRACT

BACKGROUND: The COVID-19 pandemic has led to an immense need to develop training on case recognition and management, with a focus on patients' and health professionals' safety at several levels of healthcare settings in Brazil. Different simulation strategies can be included in the diverse clinical care phases for these patients.

OBJECTIVE: To suggest a complete simulation-based training program for Brazilian hospitals and/or academic institutions at this moment of the pandemic.

DESIGN AND SETTING: Descriptive analysis on possible simulated clinical cases using different methodologies, thereby supporting suspected or confirmed COVID-19 patients.

METHODS: This was a reflective theoretical descriptive study on an educational program based on clinical simulation, with four practical phases at different performance and complexity levels. Wearing, handling and adequately disposing of personal protective equipment, along with specific respiratory procedures in different healthcare settings up to intensive care for seriously infected patients were addressed.

RESULTS: This program was designed for application at different Brazilian healthcare levels through different clinical simulation strategies. Summaries of expected performance were suggested in order to standardize technical capacity within these simulation settings, so as to serve these levels.

CONCLUSIONS: Developing training programs for situations such as the current COVID-19 pandemic promotes safety not only for patients but also for healthcare workers. In the present context, clear definition of which patients need hospital outpatient or inpatient care will avoid collapse of the Brazilian healthcare system. Institutions that do not have simulated environments can, through the examples described, adopt procedures to promote didactic information in order to help healthcare professionals during this time.

INTRODUCTION

The current global pandemic of coronavirus disease (COVID-19) has forced medical trainees throughout the world to suspend their clinical training and transition largely to online lectures. Through removing trainees from clinical settings, medical program managers hope to reduce the risk of person-to-person spread of infection.[1]

Clinical simulation has the objective of replicating scenarios that are as close as possible to reality, in order to train healthcare professionals in diverse clinical situations that demand clinical thinking, as well as simultaneous attitudinal and procedural abilities.[2]

Simulation-based medical education (SBME) is a tool within medical training that has quickly expanded in use over recent years and has enabled great advances. In particular, it has been lauded for its improvement of medical education, coupled with cost savings and protection of patients.[3]

Diverse simulated strategies can be used, depending on the expertise level of participants and the central objective at hand, as well as the availability of resources and specialists in the method and topic to be developed.[2]

Situations requiring extreme care, rare clinical cases and situations requiring emergency training are benefited through simulation strategies. These strategies take into consideration the

safety of the patients and health professionals involved, within a controlled environment, with repetition and good rates of knowledge absorption, compared with passive learning methods.[2]

COVID-19 belongs to the beta-coronavirus family. These are ribonucleic acid (RNA) viruses with high mutation rates enabling adaptation to diverse host organisms, and with fast dissemination among humans. Human-to-human transmission of COVID-19 occurs through respiratory droplets and fomites. There is also the possibility of transmission during the disease incubation period or by patients with only mild symptoms, but this remains poorly understood.[4]

The clinical presentation is similar to that of the common flu, with nonspecific symptoms that can include pyrexia (fever), indisposition, coughing, pharyngitis (sore throat) and rhinorrhea (runny nose), among others. In the majority of cases (around 80%), no special treatment will be needed. However, one in every six people who acquire COVID-19 may present the severe form of the illness, with acute airway impairment.[4]

In the current scenario, which has been declared to be a pandemic, it is mandatory that healthcare professionals are trained to deal with COVID-19 at the different levels of the healthcare system, with the aim of optimizing resources and promoting safe, high-quality care. Cases need to be registered through an electronic form within the first 24 hours from the start of clinical suspicion. Currently, there are many cases of community transmission in Brazil and it is essential that all teams are trained in order not to burden and overload the healthcare services unnecessarily, including bed and supply use, which could culminate in a chaotic healthcare situation.[5]

OBJECTIVE

To describe different clinical simulation strategies, in which the aim is to train healthcare professionals to recognize and manage COVID-19 within the Brazilian healthcare system.

METHODS

This was a reflective theoretical descriptive study on an educational program based on clinical simulation, with four practical phases at different levels of performance and complexity.

This study addressed the use of a variety of different procedures. Wearing, handling and adequately disposing of personal protective equipment (PPE) was assessed, including use of gloves, medical masks, goggles or face shields, and gowns. Equipment for specific procedures such as respirators (i.e. N95 or FFP2 standard or equivalent) and aprons was also addressed, in different healthcare settings up to intensive care for seriously infected patients.

RESULTS

This program was designed to be applied at different levels of Brazilian healthcare through different clinical simulation strategies. Summaries of expected performance were suggested in order to standardize technical capacity within these simulation settings, thus making it possible to serve the different levels of care within healthcare provision in Brazil.

Clinical simulation strategies

In starting to train the healthcare team, we considered that it was essential to standardize concepts and practice procedures using low-fidelity manikins (task trainers). In addition, there was a need for reinforcement of the following procedures: basic hand hygiene, adequate use of individual protection equipment, the notification system for suspicious cases, use of peripheral and central accesses, intraosseous puncture, orotracheal intubation, collection of secretions, use of swabs, team movement and putting patients into the prone position. These were deemed to be priorities for trained, with direct feedback.

Phase 1 considered standardized patients, and simulation was used in accordance with the local possibilities in the primary healthcare system, with a focus on anamnesis and physical examination for decision-making to recognize the disease and provide initial management. Phase 2 considered standardized patients, and simulation was used in accordance with the local possibilities in the primary or secondary healthcare system, with a focus on anamnesis and physical examination for decision-making, to recognize the disease and provide initial management. In this context, debriefing so that the participants could reflect and learn was mandatory. The rapid cycle of deliberate practices suggested in phase 3 of the training comprised simulations that were interrupted so that immediate feedback could be provided to the facilitator, with the aims of performance enhancement and allowing many repetitions.[6] In this phase, it was suggested that patients in need of hospitalization should be taken care of. Lastly, to end the training, phase 4 consisted of a classic simulation followed by debriefing, which concentrated on taking care of critical patients with deterioration of the hemodynamic situation, as presented in **Table 1**.

In situ simulation, which occurs inside the real care environment, is advisable when possible. However, the logistics for this are much more complex logistics and this can be more taxing, since the resources used in this care service are the same as what is available for real patients. In this article, the use of specific training spaces is described, in academic and hospital settings (**Figures 1** and **2**).

Scenario flowchart

The main objective of this study was to create scenarios that would prepare professionals to determine which patients present symptoms that need hospitalization, and which patients only require examinations and guidance, with reassessment if necessary.

Phase 1

Clinical case: Patient K.G.R., 43-year-old female, with fever for one day, dry cough and headache. She goes to a primary care unit for treatment.

- She says that she does not have any allergies or any routine use of medications.
- She says that she has not had any surgery or recent previous pathological conditions.
- Normal water and food intake.
- She has not traveled recently and has not been exposed to any international travelers.

Key points: Presence of fever is confirmed; anamnesis and detailed physical examination are performed; previous records and current use of medication are investigated.

Actions: Pertinent medication is prescribed; patient is advised to stay at home; no examinations using nasal and oropharyngeal swabs are requested.

Simulation: A standardized patient or a simulator that is available can be used; primary care material practice.

Debriefing: Discussion should be focused on parameters that are not criteria for hospitalization and examination requests. Communication abilities are needed for effective and clarifying

Table 1. Description of methodologies and content to be addressed during COVID-19 training

Methodology	Context	Objectives	Topics to be discussed
Phase 1: Task trainer	Specific-ability manikins for handwashing, orotracheal intubation, peripheral and central access and intraosseous puncture	Fundamental procedural review from initial to critical care management	PPEs, indications, counterindications, good practice review, COVID-19 patient intubation care and the risks of noninvasive ventilation during transmission
Phase 2: Standardized patient	To be cared for within the primary or secondary healthcare system	Triage; initial recognition and management; and knowing the parameters and actions for patients who do not need hospitalization	General parameters, anamnesis and physical examination
Phase 3: Rapid-cycle deliberate practice	Simulator for cases of medium or high levels of complexity, for initial management in an emergency care unit	Recognition and management of patients who need hospitalization; symptomatic treatment and discussion of complementary examinations	Reassessment; discussion of ventilation for adequate support; making a prognosis; and transportation to critical care unit
Phase 4: Standard simulation	Critical care patients in an intensive care unit	Critical care; circulatory repercussions; and specific actions	Discernment of differences in relation to acute respiratory distress syndrome (ARDS); avoidance of excess volume and maintenance of negative balance

PPE = personal protective equipment.

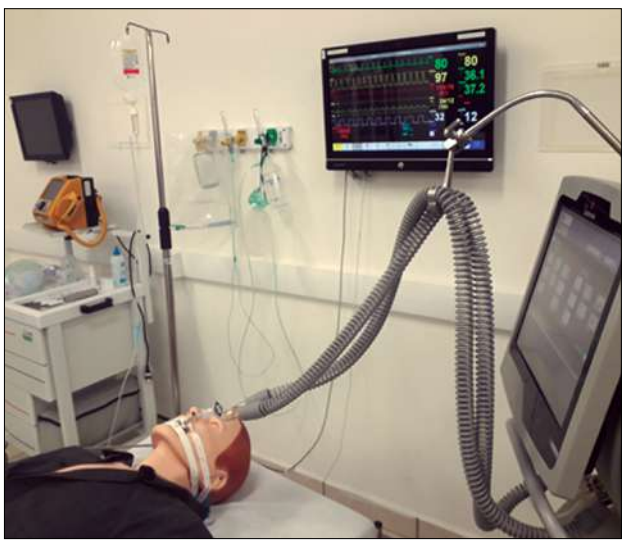


Figure 1. Example of simulation in the emergency room. Orotracheal intubation within the specifications for COVID-19 was performed.

Figure 2. Example of standard simulation. Critical patient with circulatory impairment in prone position.

orientation for patients, who will be anxious and afraid of having COVID-19.

Consider: Primary healthcare is the first point of contact with the healthcare system, for individuals, families and communities. In relation to managing COVID-19, primary healthcare needs to take on a proactive role as the care flow coordinator, i.e. to organize the actions, sequence the flow of care and its continuation, with emphasis on family and community orientation.

Phase 2

Clinical case: Patient J.F.S., 63-year-old male, with fever for one day, dry cough and coryza. He goes to a primary care unit for treatment (**Figures 3** and **4**).

- He says that he does not have any allergies, and is using beta-blockers and statins.
- He says that he has not had any surgery or recent previous pathological conditions.
- Normal water and food intake.
- He has not traveled recently and has not been exposed to any international travelers.

Key points: Presence of fever is confirmed; anamnesis and detailed physical examination are performed; previous records and current use of medication are investigated.

Actions: Pertinent medication is prescribed; patient is advised to stay at home; no examinations using nasal and oropharyngeal swabs are requested. Prescription of oseltamivir (75 mg twice a day) can be considered for this at-risk group. Reassessment orientation can be provided if necessary.

Simulation: A standardized patient or a simulator that is available can be used; primary care material practice.

Debriefing: Discussion should be focused on parameters that are not criteria for hospitalization and examination requests. Communication abilities are needed for effective and clarifying orientation for patients, who will be anxious and afraid of having COVID-19.

Consider: Classifying the severity of the patient's flu-like syndrome will define whether the patient will be kept within primary

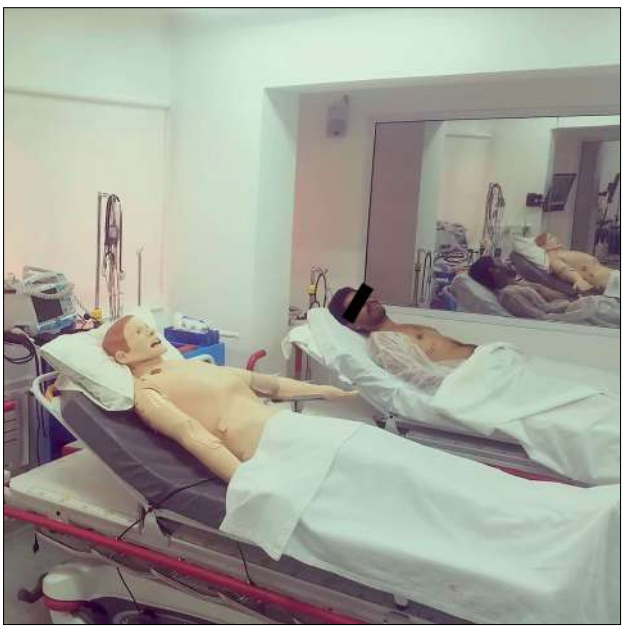


Figure 4. Example of standardized patient (actor) or simulator as an option in scenarios of Phases 1 and 2.

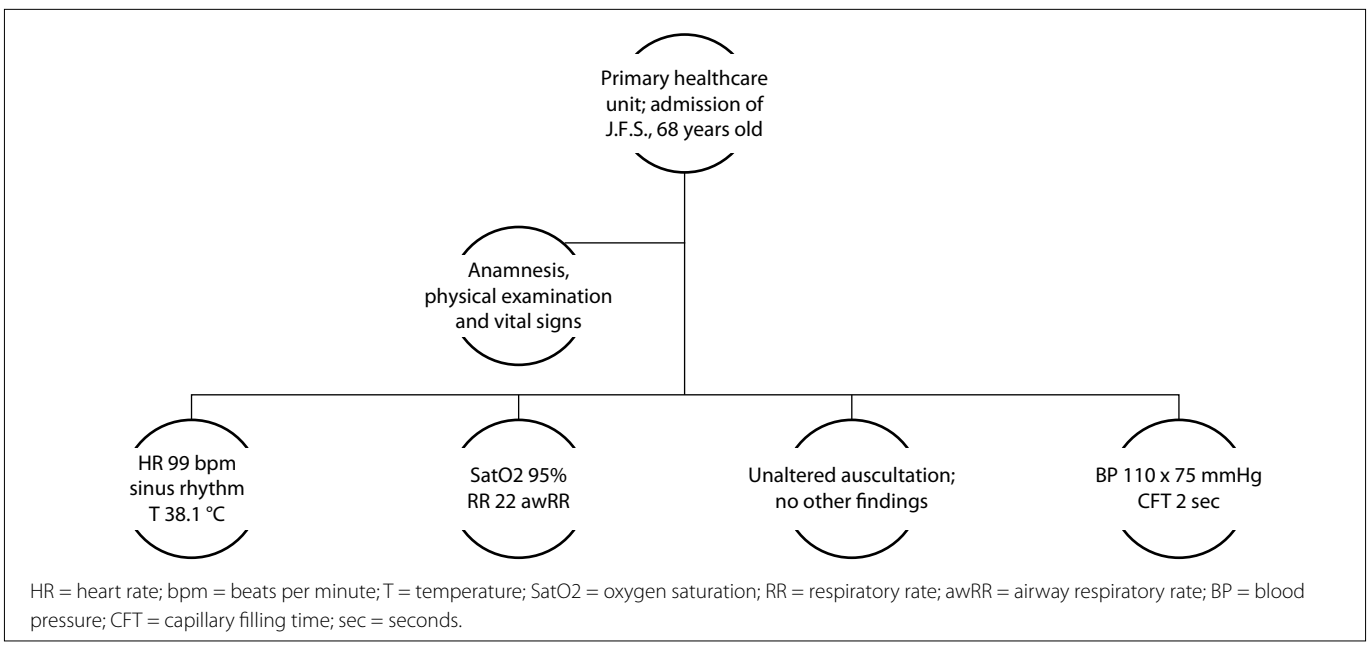


Figure 3. Initial scenario pattern in primary healthcare for Phase 2.

care or will be referred to specialist centers, emergency centers or hospitals.

Patients presenting less than 95% oxygen saturation in room air, signs of respiratory discomfort, hypotension or acute respiratory insufficiency need to be sent for specialized attention.[1]

Phase 3

Clinical case: R.T.K., 67-year-old female with fever for two days, body pain, sore throat and dry cough. She seeks medical care and treatment at a hospital outpatient clinic (**Figure 5**).

- She says that she does not have any allergies, and is using metformin hydrochloride.
- She says that he has not had any recent surgery or recent previous pathological conditions.
- Diminished water and food intake.
- She has not traveled recently and has not been exposed to any international travelers.

Key points: Need for hospitalization is identified through general assessment of the patient; need to understand which patients are at high risk; directed requests for complementary exams need to be made. Use of complementary oxygen and notification needs to be discussed.

Simulation: A medium to high-fidelity simulator in which parameters can be seen as pertinent alterations (auscultation) should be used. A medical assistance room with supplemental oxygen material is required.

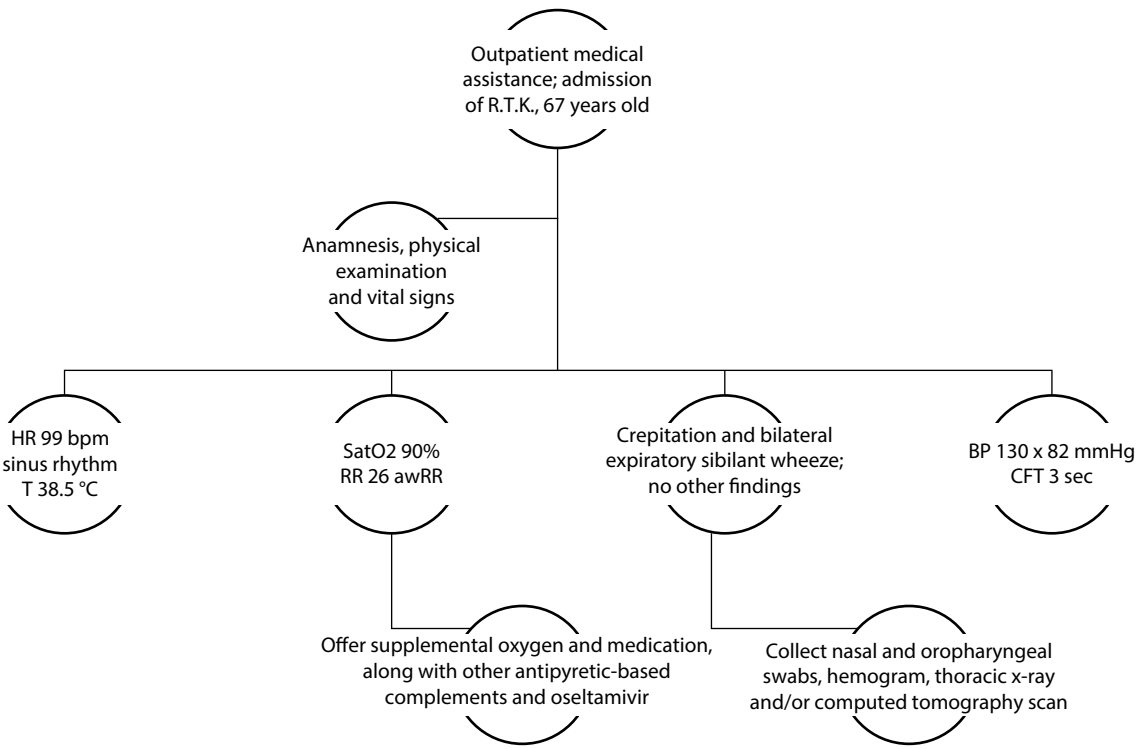
Rapid-cycle deliberate practice: The specialist will give immediate feedback regarding the participants' behavior. The discussion should focus on the parameters that are criteria for hospitalization and on understanding which specific examinations that can be requested will have prognostic value.

Phase 4

This is the same patient as in Phase 3, but with worsening of the patient's condition.

Clinical case: R.T.K. 67-year-old female with fever for two days, body pain, sore throat and dry cough. She sought medical care and treatment at a hospital outpatient clinic and was admitted to that hospital. Examinations were requested (**Figures 6** and **7**).

Key points: Her condition has worsened, with the need to ensure airway patency. Complementary examinations that can be used include: glutamic oxaloacetic transaminase (GOT), glutamic pyruvate transaminase (GPT), D-dimer, troponin, arterial blood



HR = heart rate; bpm = beats per minute; T = temperature; SatO2 = oxygen saturation; RR = respiratory rate; awRR = airway respiratory rate; BP = blood pressure;CFT = capillary filling time; sec = seconds.

Figure 5. Scenario pattern indicative of investigation and hospitalization.

gas test, urea, creatinine, sodium (Na), potassium (K), lactate dehydrogenase, C-reactive protein (CRP) and ferritin.

Simulation: A medium-fidelity or high-fidelity simulator in which parameters can be seen as pertinent alterations should be used. Laboratory tests and imaging examinations need to be made available at this stage of care, to aid in decision-making. A medical assistance room equipped with emergency care is needed.

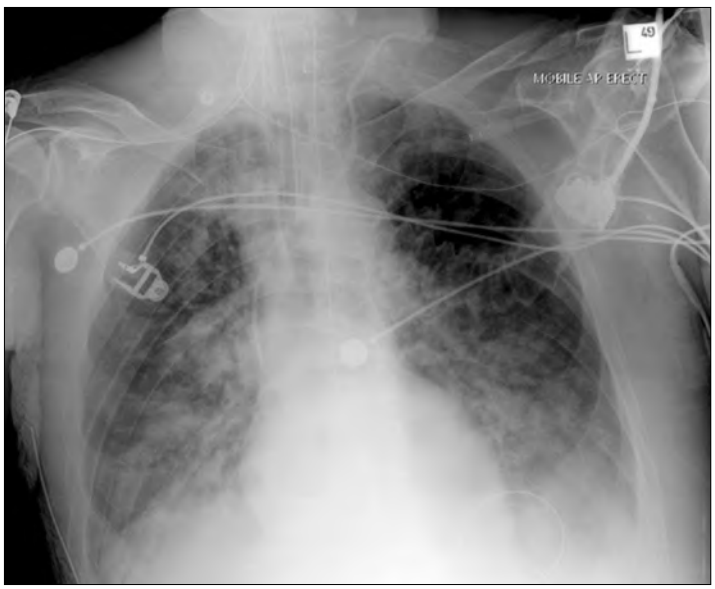


Figure 6. Chest X-ray used for COVID-19 training. Case courtesy of Prof Frank Gaillard, Radiopaedia.org.

Debriefing: The focus should be on actions to be taken before clinical deterioration, airway handling and mechanical ventilation.

Consider: The guidelines for the novel coronavirus are frequently changing, as more information about the virus is received. Hospital infection control committee recommendations regarding on prevention also vary among institutions. The most up-to-date guidelines need to be reviewed and discussed with the committee's team before executing any simulation.

Lastly, use of an tool within the checklist format to summarize the expected performance at each phase is suggested. It should be ensured that discussions become homogeneous within all groups that are trained (**Table 2**).

DISCUSSION

Within healthcare education, patient-focused learning is fundamental. It is more meaningful and more motivating than any other educational strategy.

However, safety-related issues, ethics and the need for efficient learning within a short time make clinical simulation an option that promotes contextualization, motivation, learning feedback and, especially, concrete reproduction of the applicability of the acquired knowledge. This is one of the bases of andragogy, i.e. adult education.[2]

In a recent study, a simulation mannequin was used to analyze the effectiveness of personal protective equipment (PPE) during the COVID-19 outbreak and to subsequently adjust PPE standards accordingly.[7] Simulation can be used to address issues ranging from proper donning of PPE to patient management. It allows trainees to

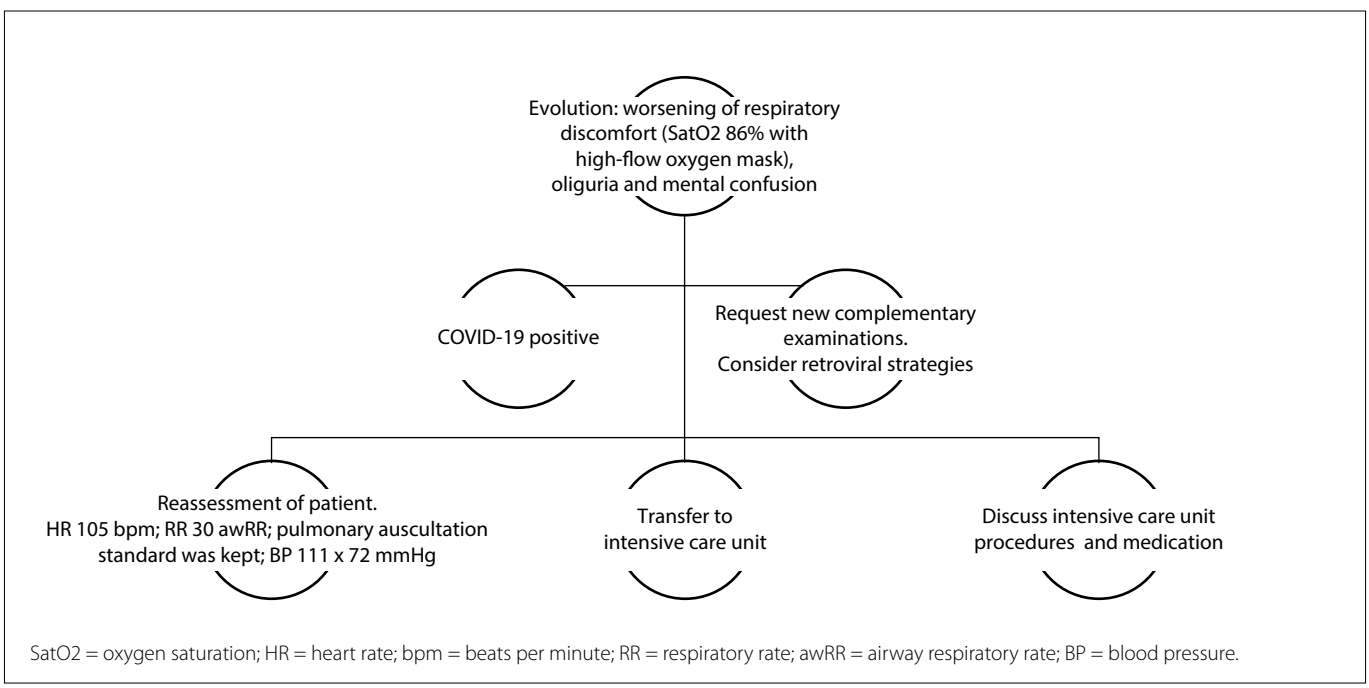


Figure 7. Initial pattern of patient in critical care.

adhere to the bans on public gatherings that are being enforced by local governments and thus enables them to continue their medical education. This can be accomplished through eliminating human contact at simulation centers, remotely distributing virtual reality technology that is currently used within anatomy education, and/or integrating virtual simulation programs into online curricula.[7]

Care provision during the COVID-19 pandemic still presents uncertainties and difficulties regarding triage, initial care and critical patient management. This justifies implementation of training based on the most relevant information on how to manage these patients. The pedagogical structure suggested here can also be used for several other situations, for training through clinical simulation.

However, one limitation of the present study relates to the dynamic course of the COVID-19 pandemic and the few education-focused published papers addressing this. Therefore, the scenarios described here may need adaptations to align them at all levels of care as new research on the conduct and protocols to be followed moves forward.

Table 2. Performance tools expected to be used within each training phase

Scenarios	Checklist
Phase 1	Patient identification Use of relevant personal protective equipment Directed anamnesis Physical examination with precautions for COVID-19 Doctor-patient communication Clinical reasoning
Phase 2	Patient identification Use of relevant personal protective equipment Directed anamnesis Physical examination with precautions for COVID-19 Doctor-patient communication Clinical reasoning Requesting and carrying out complementary examinations
Phase 3	Patient identification Use of relevant personal protective equipment Directed anamnesis Physical examination with precautions for COVID-19 Doctor-patient communication Clinical reasoning Requesting and carrying out complementary examinations Discussion of hospitalization with the patient
Phase 4:	Patient identification Use of relevant personal protective equipment Directed anamnesis Physical examination with precautions for COVID-19 Doctor-patient communication Clinical reasoning Requesting and carrying out complementary examinations Emergency airway procedure Referral to intensive care unit

CONCLUSIONS

Use of different clinical simulation strategies can contribute effectively to healthcare professionals' training at all levels of the Brazilian healthcare system. It is suggested that educational institutions should help their care partners with potential specific training as much as possible. Developing training programs in situations resembling the current COVID-19 pandemic promotes safety not only for patients but also for the professionals involved. Within the current context, determining which patients need hospital assistance or need to be hospitalized will avoid collapse of care provision. Institutions that do not have simulation environments can, through the examples described here, adopt other ways of promoting didactic information, in order to help healthcare professionals during this difficult time.

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writing-original draft (equal) and writing-review and editing (equal). This author agrees to be responsible for all aspects of this work, thus ensuring that issues relating to the accuracy or integrity of any part of it are investigated and resolved accordingly. Vaccarezza GF: conceptualization (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), supervision (equal), validation (equal), writing-original draft (equal) and writing-review and editing (equal). Bizario JCS: conceptualization (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal). Gois AFT: conceptualization (equal), formal analysis (equal), methodology (equal), project administration (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal). All authors approved the final version for publication

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Address for correspondence:
Carolina Felipe Soares Brandão
Universidade Municipal de São Caetano do Sul (USCS)
R. Santo Antonio, 50
São Caetano do Sul (SP) — Brasil
CEP 09521-160
Tel. (+55 11) 42393378
E-mail: carolinafs11@gmail.com

Can p63 serve as a biomarker for diagnosing giant cell tumor of bone? A systematic review and meta-analysis

Zihao Wan[I], Chien-Wei Lee[II], Shuai Yuan[III], Oscar Kuang-Shen Lee[IV]

Hong Kong Special Administrative Region, China

[I]MD. Doctoral Student, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong, China.
orcid.org/0000-0002-7538-1018

[II]PhD. Research Associate Professor, Institute for Tissue Engineering and Regenerative Medicine, The Chinese University of Hong Kong; and Research Associate Professor, School of Biomedical Science, The Chinese University of Hong Kong, Hong Kong, China.
orcid.org/0000-0002-6679-0020

[III]MSc. Doctoral Student, Cardiovascular and Nutritional Epidemiology Unit, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.
orcid.org/0000-0001-5055-5627

[IV]MD, PhD, Professor, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong; Professor, Institute for Tissue Engineering and Regenerative Medicine, The Chinese University of Hong Kong; and Professor, Li Ka Shing Institute of Health Sciences, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China.
orcid.org/0000-0003-3847-7085

KEY WORDS (MeSH terms):
Biomarkers.
Diagnosis.
Giant cell tumor of bone.

AUTHORS' KEY WORDS:
p63.
Benign tumor.
GCTB.

ABSTRACT

BACKGROUND: Tumor protein p63 (p63) has been reported to be highly expressed in giant cell tumor of bone (GCTB). Whether p63 can be treated as a diagnostic marker for GCTB remains unclear.

OBJECTIVE: We conducted a meta-analysis to evaluate the applicability of p63 in diagnosing GCTB.

DESIGN AND SETTING: Systematic review and meta-analysis carried out in a public hospital, Hong Kong, China.

METHODS: We searched PubMed, EMBASE and the Cochrane Library from inception to April 30, 2019. Literature in English or Chinese about the differential diagnosis of GCTB using p63 were included. Animal experiments, reviews, correspondence, case reports, expert opinions and editorials were excluded. Studies were also excluded if they did not provide sufficient information to construct a 2×2 contingency table. We calculated individual and pooled sensitivities and specificities. We used I^2 as an indicator of heterogeneity.

RESULTS: Out of 88 records identified, 8 articles on 788 GCTB patients fulfilled the inclusion criteria and were included in the present analysis. Bivariate analyses yielded a pooled mean sensitivity of 0.87 (95% confidence interval, CI, 0.72-0.95) and specificity of 0.71 (95% CI, 0.56-0.82) for using p63 as a biomarker in diagnosing GCTB. The area under the receiver operating characteristic curve was 0.86 (95% CI, 0.82-0.88).

CONCLUSION: p63 is a helpful indicator in diagnosing GCTB due to its high sensitivity and specificity. Nonetheless, the results need to be carefully interpreted based on other diagnostic methods such as imaging.

SYSTEMATIC REVIEW REGISTRATION: 164115 (PROSPERO registration number)

INTRODUCTION

Giant cell tumor of bone (GCTB) is the prototype of giant cell-rich neoplasms of the skeleton, representing 4% to 5% of all primary bone tumors. GCTB mainly occurs in skeletally mature patients, with a peak incidence between ages 20 and 45 years and slight predominance among females.[1-3] GCTB commonly arises at the epiphyses of long bones, like the distal femur, proximal tibia, distal radius and proximal humerus.[4] In addition, it is often found close to joints, and therefore causes movement limitation, joint effusion and synovitis.

At the time of diagnosis, approximately 12% of patients with GCTB present with pathological fractures.[5,6] These tumors are locally aggressive with a tendency to recur.[7,8] Lung metastases occur infrequently.[9,10] The typical appearance of GCTB is best demonstrated on conventional radiographs, which show a lytic lesion that has a well-defined but nonsclerotic margin, is eccentric in location, extends to the subchondral bone and occurs in patients with a closed physis.[11-13] The tumor component is heterogenetic. There are mainly three types of cells in the tumor, including osteoclast-like giant cells, macrophage-like cells and stromal cells. Stromal cells are considered to be the neoplastic component of GCTB.[12,14,15]

The diagnosis of GCTB is based not only on histology but also on clinical and radiological data.[16] GCTB is usually a solid mass and brownish in color. Typically, it is characterized by abundant osteoclast-like giant cells surrounded by spindle cells in histological appearance. Usually, a planned biopsy for GCTB is the gold standard for pathological assessment. While the diagnosis is often straightforward, it can be challenging with small core needle biopsies, particularly when dealing with unusual sites or skeletally immature patients.[17]

p63 belongs to the family of transcription factors that also includes p53 and p73.[18] Giant cells are demarcated through CD63 immunohistochemical staining. This staining basically marks osteoclastic giant cells and macrophages and indicates that these cells originate from the monophagocytic-macrophagocytic system.[18] It is mostly used as a diagnostic aid in cases of breast,

prostate and salivary gland cancer because of its high sensitivity and specificity for mammary and salivary myoepithelial cells and prostatic basal cells.[19,20,18] p63 has also been identified as highly expressed in GCTB, but opinions regarding the usefulness of p63 as a diagnostic marker for the disease have been divergent.[19,18]

OBJECTIVE

The objective of this study was to summarizes the current evidence for validation of the diagnostic value of p63 in cases of GCTB.

METHODS

Search strategy and selection criteria

We systematically searched PubMed, Embase and the Cochrane Library (from inception to April 30, 2019) for studies assessing the accuracy of p63 as a diagnosis indicator of GCTB. The search strategy is shown in **Table 1**. We also reviewed the reference lists of each primary study identified and of previous systematic reviews. English and Chinese language restrictions were imposed.

Studies were included if they met following criteria: (1) they assessed the accuracy of p63 for diagnosing GCTB; (2) the gold standard was histological diagnosis; and (3) sufficient information to construct a 2×2 contingency table was provided. Animal experiments, reviews, correspondence, case reports, expert opinions and editorials were excluded.

Data extraction was performed by two reviewers independently. Disagreements were resolved by reaching a consensus or through discussion among the coauthors. The extracted data comprised the general and detailed methodological characteristics, characteristics of the study population, details of the p63 assays and the numbers of true and false positives and negatives.

All studies included in the diagnostic review were assessed for methodological quality using the QUADAS-2 measurement of bias and applicability, by two reviewers, and any disagreements were resolved through reaching a consensus.

Table 1. Search strategy

Database	Search terms	Results
MEDLINE-PubMed (1950-April 30, 2019)	(((((“Giant Cell Tumors”[Mesh]) OR “Giant Cell Tumor of Bone”[Mesh])) AND ((“TP63 protein, human” [Supplementary Concept]) OR P63))) OR (((((giant) AND cell) AND tumor)) AND ((“TP63 protein, human” [Supplementary Concept]) OR P63))	51 studies
EMBASE (1946-April 30, 2019)	1. giant AND cell AND tumor 2. p63 OR TP63 3. (1) and (2)	33 studies
Cochrane Library (inception) to April 30, 2019	1. GIANT and CELL and TUMOR:ti,ab,kw (Word variations have been searched) 2. "p63" or "TP63":ti,ab,kw (Word variations have been searched) 3. (1) and (2)	4 studies

Statistical analysis

We tabulated true positives, false negatives, false positives and true negatives among patients with GCTB, stratified according to study, and calculated the sensitivity and specificity and corresponding confidence interval (CI). To synthetize the data, we used an exact binomial rendition of the bivariate mixed-effects regression model for meta-analyses on treatment trials, with modification for synthesis of diagnostic test data.[21-24] This model does not transform pairs of sensitivity and specificity of individual studies into a single indicator of diagnostic accuracy, but it preserves the two-dimensional nature of the data and takes into account any correlation between the two.

We estimated mean logit sensitivity and specificity with their standard error and 95% CIs, the between-study variability in logit sensitivity and specificity, and the covariance. We back-transformed these quantities to the original receiver operating curve scale to obtain summary sensitivity and specificity, and diagnostic odds ratios. We then used the derived logit estimates of sensitivity and specificity, and their respective variances, to construct a hierarchical summary receiver operating curve for p63 with summary operating points for sensitivity and specificity on the curves and a 95% confidence contour ellipsoid (two-dimensional CI).

We calculated I^2 to assess heterogeneity. If heterogeneity among studies was recorded, the potential source of heterogeneity was investigated through subgroup analysis. To investigate publication bias, we constructed effective sample size funnel plots versus the log diagnostic odds ratio and did a regression test on asymmetry.[25]

The MIDAS module 22 was used in the bivariate summary receiver operating curve analysis. We used the MIDAS module and the Quality Assessment of Diagnostic Accuracy Studies module to evaluate the quality of the studies included. All analyses were performed in the STATA software (version 15.1, StataCorp, Texas, United States).

RESULTS

Out of the 88 articles retrieved, 76 papers were excluded after duplicates, titles and abstracts had been assessed. We further excluded four papers after full-text reviewing, thus leaving eight studies in the present analysis (**Figure 1**). The result from the quality assessment is shown in **Figure 2**.[15,18,20,26-30]

Table 2 shows the characteristics of the eight studies included. In total, 788 critically ill patients were included in the analysis, of whom 335 (42.5%) suffered from GCTB. The prevalence of GCTB among the studies ranged from 6.6% to 86.8% (mean of 42.5%).[15,18,20,26-30]

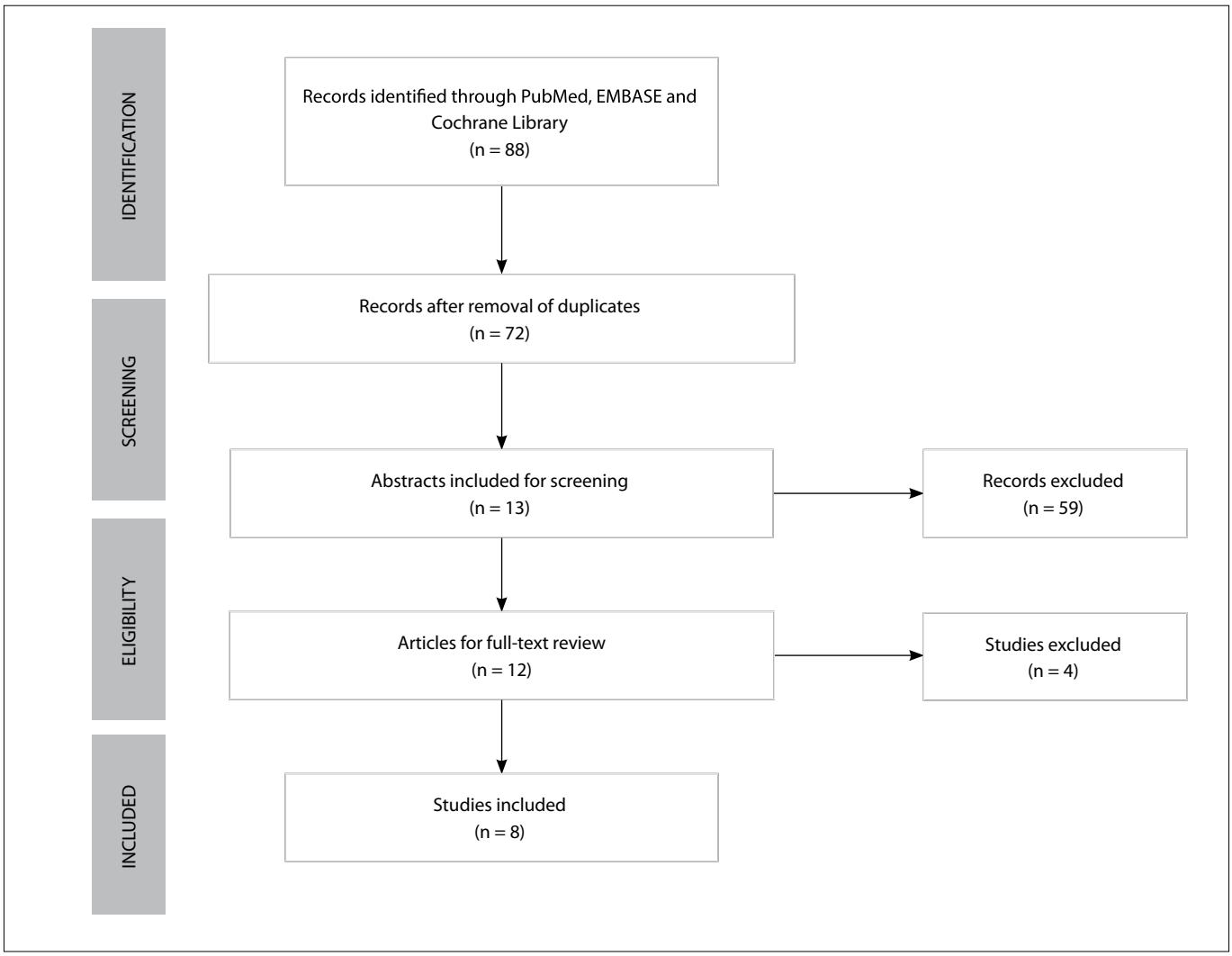

Figure 1. Study selection process.

No publication bias was identified through Deeks' regression test of asymmetry (t = 1.24; P = 0.26; **Figure 3**).[15,18,20,26-30] The pooled sensitivity of p63 was 0.87 (95% CI, 0.72-0.95) and the specificity was 0.71 (95% CI, 0.56-0.82), as an indicator in making the diagnosis of GCTB (**Figure 4**). The area under the receiver operating characteristic curve was 0.86 (95% CI, 0.82-0.88) (**Figure 5**). We detected substantial significant heterogeneity among the studies included (overall I^2, 90%; 95% CI, 80-100). The samples included were stratified according to gender, age range, complications and lesion sites, if information relating to these factors was available. However, no subgroup analysis could explain the significant heterogeneity.

In our study, both the likelihood ratio and the post-test probability were moderate (**Figure 6**).

Given a pretest probability of 42%, the post-test probability for a positive test result is 69%. Likewise, a negative likelihood ratio of 0.18 reduces the post-test probability to 12% for a negative test result.

DISCUSSION

There are multiple giant-cell-rich bone tumors that can express p63, although the expression level varies. However, there is no consensus regarding the p63 expression level of GCTB clinically.[1,18,20] Researchers or clinicians have proposed that a certain percentage of p63 expression in giant cells can be used as a cutoff value in making the diagnosis of GCTB.[28] Maues De Paula et al.[28] declared that a finding of more than 50% of the cells positive for p63 was highly related to a diagnosis of GCTB while percentages lower than 50% appeared to be nonspecific. Nevertheless, we are unable to define a cutoff value for p63 expression levels because of discrepancies in the standards used for evaluating p63 expression between the different studies.

Likelihood ratios and post-test probabilities are also relevant for clinicians. They provide information about the likelihood that a patient with a positive or negative test actually has GCTB or not.

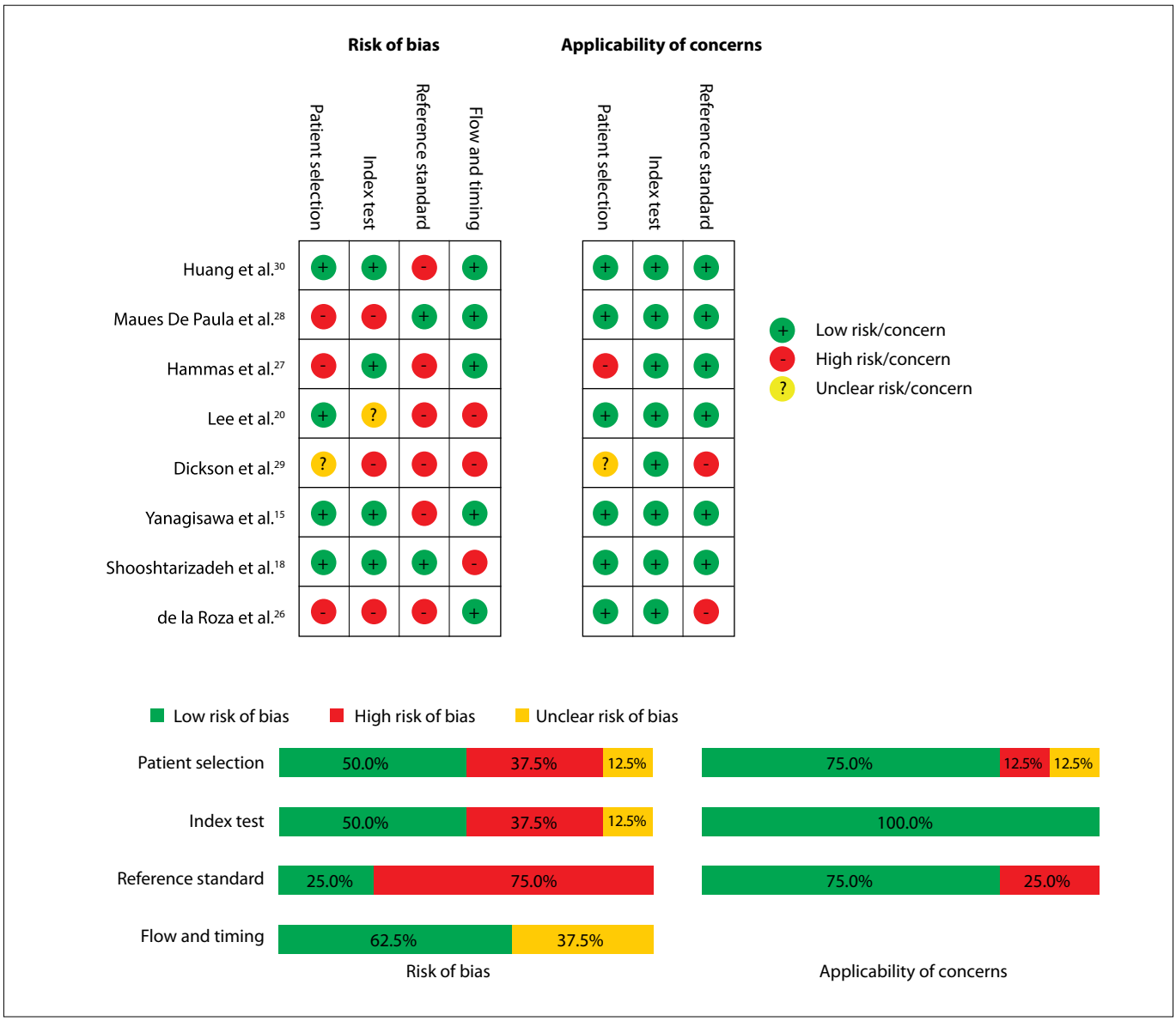

Figure 2. Quality assessment.

Table 2. Diagnostic accuracy results

Authors	Year	n	TP	FN	Sensitivity (95% CI)	FP	TN	Specificity (95% CI)
Huang et al.[30]	2014	136	99	19	0.84 (0.76-0.90)	3	15	0.83 (0.59-0.96)
Maues De Paula et al.[28]	2014	272	98	21	0.82 (0.74-0.89)	72	81	0.53 (0.45-0.61)
Hammas et al.[27]	2012	48	5	0	1.00 (0.48-1.00)	20	23	0.53 (0.38-0.69)
Lee et al.[20]	2008	91	5	1	0.83 (0.36-1.00)	13	72	0.85 (0.75-0.92)
Dickson et al.[29]	2008	46	17	0	1.00 (0.80-1.00)	5	24	0.83 (0.64-0.94)
Yanagisawa et al.[15]	2013	36	6	10	0.38 (0.15-0.65)	2	18	0.90 (0.68-0.99)
Shooshtarizadeh et al.[18]	2016	100	30	1	0.97 (0.84-1.00)	24	45	0.65 (0.53-0.76)
de la Roza[26]	2011	59	20	3	0.87 (0.66-0.97)	22	14	0.39 (0.23-0.57)
Total		**788**	**280**	**55**		**161**	**292**	

TP = true positive; FN = false negative; FP = false positive; TN = true negative; CI = confidence interval.

A certain positive likelihood ratio indicates that a person with disease is a certain number of times more likely to have a positive test result than is a healthy person. However, these likelihood ratios are calculated from dichotomized data. The result from the p63 test is either positive or negative. The disadvantage of making data dichotomous is that useful information is lost.[31] Because p63 expression levels rise as disease severity advances, patients with a high p63 expression level are more likely to be diagnosed with GCTB than are patients with a low p63 expression level.[15] To provide more precise information about the reliability of the test, we suggest that likelihood ratios should be calculated based on multiple cutoffs.

As our results show, p63 is not a single definitive diagnostic marker for diagnosing GCTB. GCTB is a pathophysiological process rather than a specific syndrome and is too complex to be described through a single measurement. Nevertheless, p63 is one of the most promising parameters.

There are several limitations to the present meta-analysis. First, we detected substantial heterogeneity between studies. However, subgroup analysis did not find any source of heterogeneity. The unrecorded differences between the studies probably contributed to the heterogeneity. Second, a reliable test for infection is still under investigation, so observational studies are biased through the choice of gold standard. Third, most of the studies included did not provide detailed information about the treatments received,

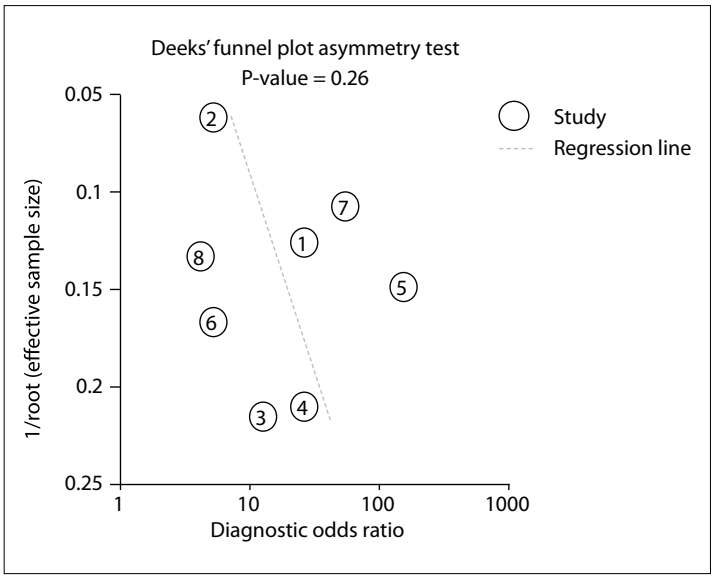

Figure 3. Deeks' funnel plot asymmetry test for publication bias.

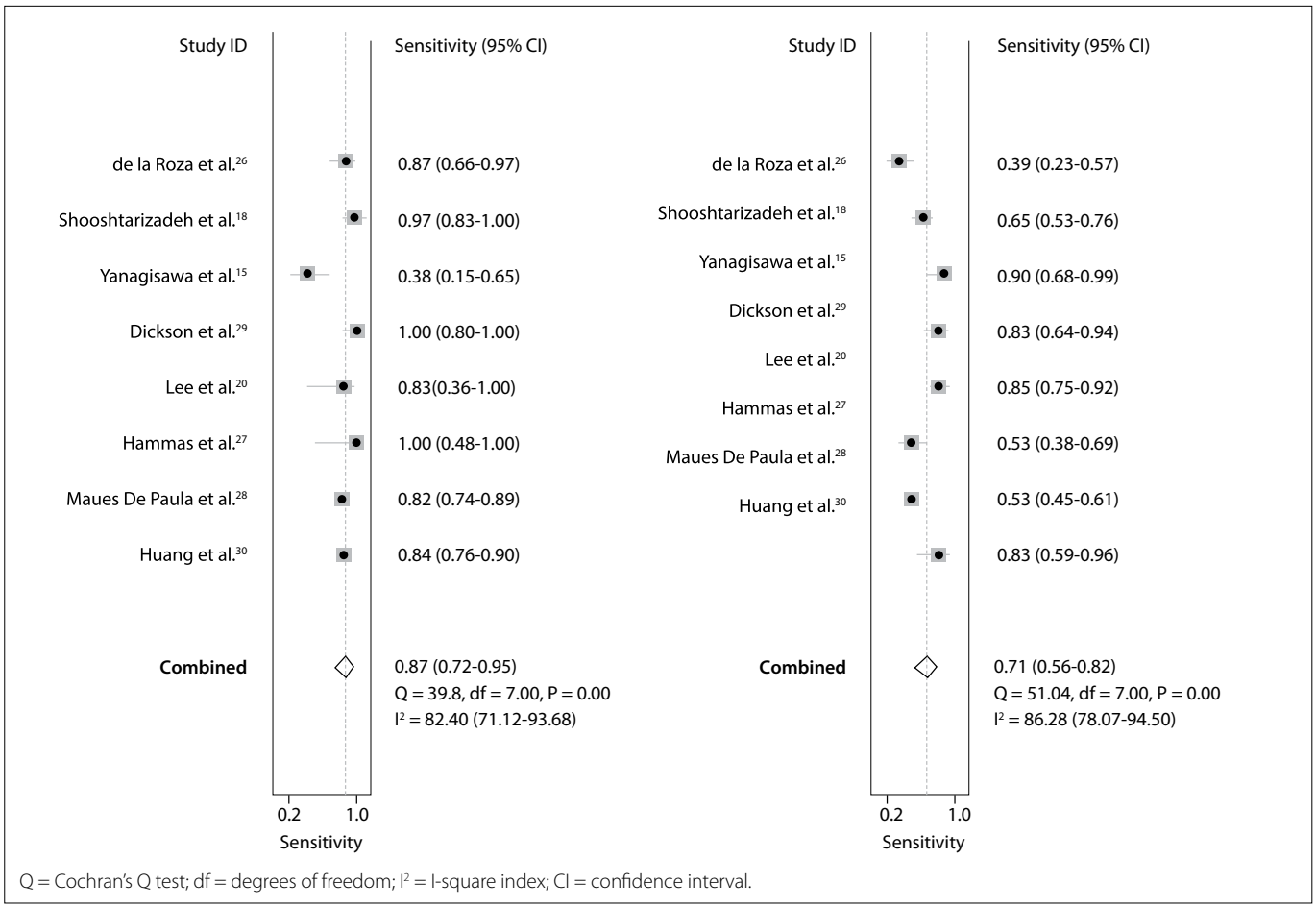

Figure 4. Sensitivity and specificity of p63 test for diagnosis of giant cell tumor of bone (GCTB).

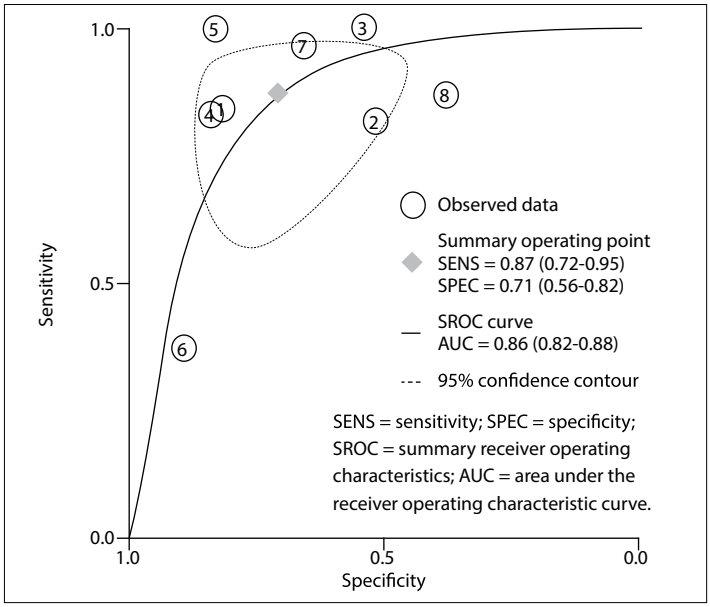

Figure 5. Summary receiver operating characteristic curve.

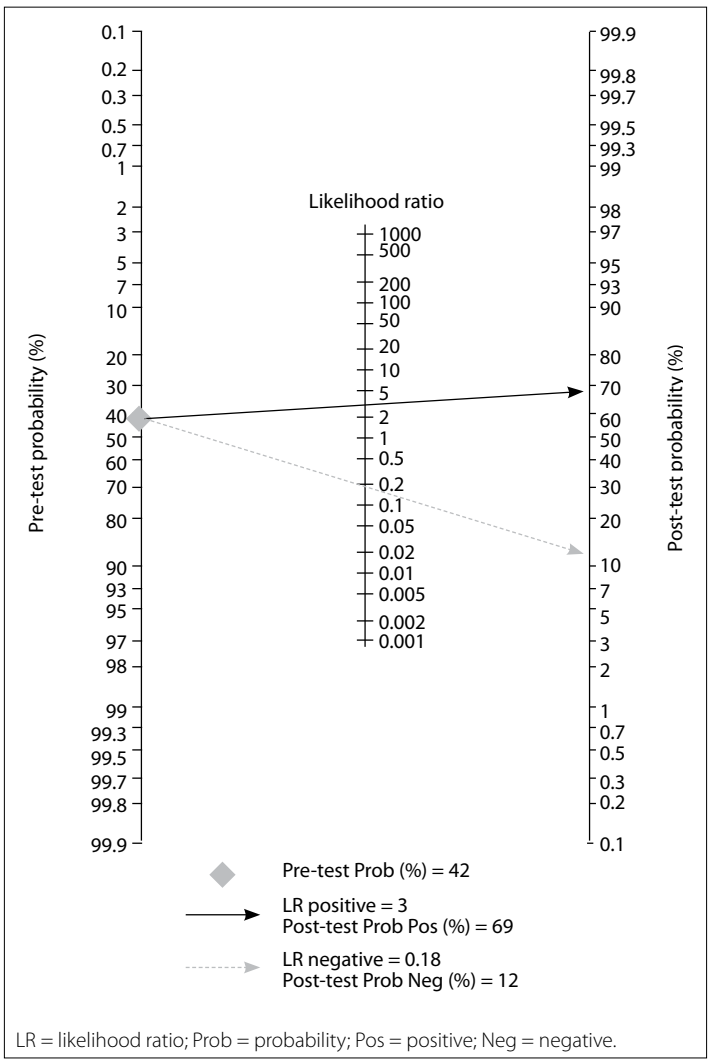

Figure 6. Fagan nomogram of the p63 test for diagnosis of giant cell tumor of bone (GCTB).

disease stages and recurrence situation. Absence of detailed patient histories could cause interobserver variability, which could lead to false-negative or false-positive judgments about the patient's medical condition. Lastly, we only included studies published in English, which also may potentially have caused bias through the language restriction in this specific systematic review.

CONCLUSION

p63 is a helpful marker for diagnosing GCTB in critically ill patients. However, it cannot be recommended as the single definitive test for making this diagnosis. The results need to be carefully interpreted in conjunction with other diagnostic methods such as imaging studies. Moreover, continuing re-evaluation of p63 during the course of the disease is warranted.

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Address for correspondence:
Oscar Kuang-Sheng Lee
Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, 30-32 Ngan Shing Street, Sha Tin, Hong Kong Special Administrative Region, 999077, China
Tel. (+852) 35052730
E-mail: oscar.lee@cuhk.edu.hk

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Structural validity of the Brazilian version of the Western Ontario and McMaster Universities Osteoarthritis Index among patients with knee osteoarthritis

Cheila de Sousa Bacelar Ferreira[I], Almir Vieira Dibai-Filho[II], Davi Oliveira da Silva Almeida[III], Daniela Bassi-Dibai[IV], Felipe Souza Barreto[V], Adriano Rodrigues de Oliveira[VI], Cid André Fidelis-de-Paula-Gomes[VII]

Postgraduate Program on Rehabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil

[I]PT. Master's Student, Postgraduate Program on Rehabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
orcid.org/0000-0001-9031-5396

[II]PhD. Professor, Postgraduate Program on Physical Education, Universidade Federal do Maranhão (UFMA), São Luís (MA), Brazil.
orcid.org/0000-0001-5403-8248

[III]Physical Education Teacher and Master's Student, Postgraduate Program on Rehabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
orcid.org/0000-0001-9153-6123

[IV]PhD. Professor, Postgraduate Program on Programs Management and Healthcare Services, Universidade Ceuma, São Luís (MA), Brazil.
orcid.org/0000-0002-6140-0177

[V]PT. Master's Student, Postgraduate Program on Physical Education, Universidade Federal do Maranhão (UFMA), São Luís (MA), Brazil.
orcid.org/0000-0002-8998-4776

[VI]PhD. Professor, Department of Physical Therapy, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
orcid.org/0000-0002-7848-7686

[VII]PhD. Professor, Postgraduate Program on Rehabilitation Sciences, Universidade Nove de Julho (UNINOVE), São Paulo (SP), Brazil.
orcid.org/0000-0001-6627-7537

KEY WORDS (MeSH terms):
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Pain.
Rheumatology.

AUTHORS' KEY WORDS:
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Confirmatory factor analysis.
WOMAC.

BACKGROUND: The original structure of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been contested in several languages.

OBJECTIVE: To assess the structural validity of the Brazilian version of WOMAC among patients with knee osteoarthritis.

DESIGN AND SETTING: Structural validity study conducted at physiotherapy clinics and primary healthcare units.

METHODS: The study included males and females aged 40 to 80 years who were all native Brazilian Portuguese speakers, with knee pain in the previous six months and a diagnosis of knee osteoarthritis. We used exploratory factor analysis (EFA) followed by confirmatory factor analysis (CFA) with implementation of a polychoric matrix and the robust diagonally weighted least squares (RDWLS) extraction method. The adequacy of the model was assessed using the following fit indices: root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI), standardized root mean square residual (SRMR) and chi-square/degree of freedom (DF).

RESULTS: 203 patients with knee osteoarthritis were included. The model proposed in this study with two factors, i.e. "pain" (items 1, 2, 3 and 4) and "physical function" (items 10, 11, 16, 17, 18, 19, 21 and 22), showed adequate fit indices in CFA: chi-square/DF = 1.30; CFI = 0.976; TLI = 0.970; RMSEA = 0.039; and SRMR = 0.070. The factorial loads ranged from 0.68 to 0.76 for the "pain" domain and 0.44 to 0.62 for the "physical function" domain.

CONCLUSION: The Brazilian version of WOMAC with two domains, i.e. "pain" (four items) and "physical function" (eight items), presents the best structure.

INTRODUCTION

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a patient-based self-report instrument that was created and validated in English in 1988, to measure pain, joint stiffness and physical function among patients with hip or knee osteoarthritis. This initial study involved face, content and construct validity, reliability and responsiveness.[1]

Since its creation, WOMAC has been translated, adapted and validated for use in several other languages, such as German, Spanish, Japanese, Swedish and Arabic.[2] There is also a Brazilian Portuguese language version but, curiously, the study in which the translation, cross-cultural adaptation and validation were performed was not published in a peer-reviewed scientific journal (it was a master's dissertation). However, adequate values for reliability and construct validity were identified.[3]

In that version of WOMAC in Brazilian Portuguese, the structural validity of the questionnaire was not ascertained. In other languages, some studies have investigated the structural validity of WOMAC by means of factor and Rasch analysis. According to a systematic review published in 2015,[2] factor analysis was conducted in five studies and variation from three to seven in the number of WOMAC domains was observed. Bilbao et al.[4] highlighted that the Spanish structure of WOMAC with three domains and 24 items was inadequate and proposed a short version with two domains and 11 items, through using confirmatory factor analysis. Rothenfluh et al.[5] used Rasch analysis and proposed a German version of WOMAC with one domain and 12 items.

Also using Rasch analysis, Davis et al.[6] proposed a new English version of WOMAC with two domains and 17 items.

Thus, considering the different investigations conducted and the different scientific conclusions reached regarding the structure of WOMAC, our study was justified by the need to identify whether the original structure of WOMAC, as used in its translation into the Brazilian Portuguese language, is adequate.

OBJECTIVE

The aim of this study was to assess the structural validity of the Brazilian version of WOMAC, among patients with knee osteoarthritis.

METHODS

Ethical aspects

This study was based on secondary analysis on data from previous studies.[7,8] It included participants who had been excluded from these previous studies, but who presented eligibility for the present study. The study procedures were approved by our institution's research ethics committee, under opinion report number 24568013.0.0000.5511, on February 10, 2014. The subjects' participation in the previous studies had been authorized and validated through their signing of an official document.

Sample

The sample size calculation for the present study was based on the recommendations of the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN), i.e. seven patients for each questionnaire item, thus resulting in a minimum of 168 patients for WOMAC.[9]

All participants in this study were recruited from the waiting lists of two physiotherapy clinics and five primary healthcare units in the city of São Paulo (SP), Brazil. The study included males and females aged 40 to 80 years who were native Brazilian Portuguese speakers, with knee pain in the previous six months and a diagnosis of knee osteoarthritis based on the criteria established by the American College of Rheumatology, with radiographic confirmation of the diagnosis.[10] These diagnoses of knee osteoarthritis were made through examination and the written opinion of a physician who was a specialist in rheumatic diseases. The exclusion criteria comprised a history of knee trauma, cognitive impairment, several psychiatric conditions (delirium, neurocognitive disorders or schizophrenia), neurological disorder (sensory or motor) or other disorders of the lower limbs that compromised their functioning.

WOMAC

This study used the WOMAC version with Likert scale responses. As in the study conducted by Fernandes,[3] the Brazilian Portuguese version has three domains, namely: "pain" domain with five items (items 1, 2, 3, 4 and 5); "stiffness" domain with two items (items 6 and 7); and "physical function" domain with 17 items (items 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24). For each item, there are five possible answers, ranging from 0 to 4. The score for each domain is calculated as the simple sum of the items answered: in the "pain domain", the score ranges from 0 to 20; in the "stiffness" domain, the score ranges from 0 to 8; and in the "physical function" domain, the score ranges from 0 to 68 points.

In the original version, the reliability found was considered adequate, with an intraclass coefficient correlation ranging from 0.73 to 0.97. Regarding the construct validity, there was an adequate correlation between the WOMAC domains and the Visual Analogue Scale, Health Assessment Questionnaire and Lequesne Algofunctional Index, with correlation magnitudes ranging from 0.425 to 0.935.

Statistical analysis

To identify the best WOMAC structure for its version in the Brazilian Portuguese language, exploratory factor analysis (EFA) was initially used, with implementation of a polychoric matrix and the robust diagonally weighted least squares (RDWLS) extraction method, since the response possibilities for each item of WOMAC are ordinal values.[11,12] The number of factors to be retained was identified and defined by means of parallel analysis with random permutation of the observed data. The rotation used was robust promin.[13,14] Data processing was performed using the free software FACTOR (Universitat Rovira i Virgili, Tarragona, Spain). The adequacy of the model was assessed using Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity. KMO values above 0.70 and significant P-values in Bartlett's test were considered adequate.[15,16]

Confirmatory factor analysis (CFA) was performed using the R Studio software (Boston, MA, USA) via its lavaan and semPlot packages. The WOMAC questionnaire is scored on a Likert scale (ordinal data). Thus, the CFA was performed with implementation of a polychoric matrix and the RDWLS extraction method, which is more suitable for ordinal variables than the maximum likelihood method.[11,17] The model fit was assessed using the following indices: root mean square error of approximation (RMSEA) with 90% confidence interval (CI); comparative fit index (CFI); Tucker-Lewis index (TLI); standardized root mean square residual (SRMR); and chi-square/degree of freedom (DF).

In the present study, values greater than 0.90 were considered adequate according to the CFI and TLI, and values less than 0.08 were considered adequate according to the RMSEA and SRMR. Values below 3.00 were considered adequate in interpreting the chi-square/DF data.[18,19] In CFA, factorial loads greater than or equal to 0.40 were considered adequate for the domain. The Akaike information criterion (AIC) and Bayesian information criterion

(BIC) were used to compare the models, and the lowest value was considered to be the most appropriate.

RESULTS

This study included 203 patients with knee osteoarthritis. The personal and clinical characteristics are described in **Table 1**. In our sample, most of the patients were elderly, female and overweight.

The EFA was carried out to explore and identify the structure of the Brazilian version of WOMAC. By means of parallel analysis, two factors were identified: the "pain" domain (items 1 to 5) and the "physical function" domain (items 6 to 24). This WOMAC structure was called Model 1. The EFA with parallel analysis presented suitable fit indices: KMO = 0.75 and Bartlett's test with $P < 0.001$. **Figure 1** presents the scree plot of this parallel analysis with the two factors defined.

From this parallel analysis, we defined Model 2 using the following procedures: items with factorial loads less than 0.50 were excluded (items 6, 7, 8, 9, 12, 13, 14, 15, 20, 23 and 24); item 5 was also excluded because it was originally created for the "pain" domain, but the factorial load of this item allocated it to the "physical function" domain (cross-loading). Therefore, Model 2 was composed of two factors: "pain" (items 1, 2, 3 and 4) and "physical function" (items 10, 11, 16, 17, 18, 19, 21 and 22).

Next, CFA was performed on Model 1 and Model 2. In addition, CFA was performed on the original version conducted by Fernandes[3] (Model 3) and on the short-form WOMAC proposed by Bilbao et al.[4] (Model 4). Among these structural models for WOMAC tested here, Model 2 presented the most adequate values for the fit indices and the lowest values of AIC and BIC, as shown in **Table 2**. The factorial loads for WOMAC with the structure of Model 2 are presented in **Figure 2**, ranging from 0.68 to 0.76 for the "pain" domain and from 0.44 to 0.62 for the "physical function" domain. The version of WOMAC with the most suitable structure is shown in **Appendix 1**.

Table 1. Characteristics of the study sample (n = 203)

Characteristics	Mean (standard deviation) or n (%)
Age (years)	66.89 (4.56)
Gender	
Male	18 (8.9%)
Female	185 (91.1%)
Weight (kg)	71.53 (4.97)
Height (m)	1.65 (0.06)
Body mass index (kg/m²)	26.23 (2.75)
Numerical pain rating (0-10)	6.57 (1.10)
WOMAC (2 domains, 12 items)	
Pain (0-16)	11.95 (1.81)
Physical function (0-32)	24.18 (2.77)

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

DISCUSSION

Our study revealed that the most suitable structure for WOMAC in Brazilian Portuguese has two domains: four items in the pain domain (items 1, 2, 3 and 4) and eight items in the physical function domain (items 10, 11, 16, 17, 18, 19, 21 and 22). The structural validity of WOMAC has been tested in several studies. According to a systematic review conducted by Gandek,[2] EFA was carried out on four studies,[20–23] and the number of factors (domains) retained for the English and Chinese versions of WOMAC were 3, 4, 5 and 7. This number of domains was higher than the two found in the present study.

We emphasize that our study used parallel analysis as the factor retention method, whereas the abovementioned EFA used other methods for such purposes. Currently, parallel analysis is considered to be a more adequate and robust method for identifying the number of factors in a questionnaire.[24,25] Another positive point of the present study is that we implemented factor analysis based on a polychoric matrix and we used RDWLS as an extraction method. These implementations are appropriate and should be used for ordinal categorical data, as in the case of the Likert scale (0, 1, 2, 3 and 4).[11,12]

In addition to the studies cited in the systematic review conducted by Gandek,[2] the original WOMAC structure with three domains and 24 items has been rejected by other authors who used the Rasch analysis. Davis et al.[6] included patients before and after total hip or knee arthroplasty and identified two domains as the best WOMAC structure in English: pain (three items) and physical function (14 items). Another study that investigated the structure of the German version of WOMAC included patients with femoroacetabular impingement and hip osteoarthritis. These authors established a one-dimensional structure for WOMAC with 12 items as the appropriate option.[5]

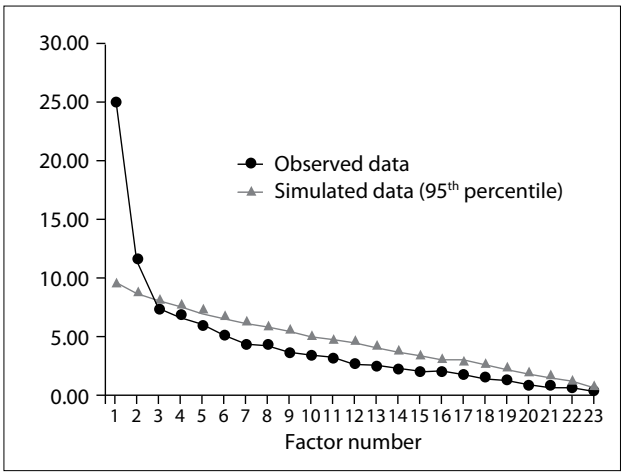

Figure 1. Scree plot from parallel analysis.

Table 2. Confirmatory factor analysis on the four structures of the Western Ontario and McMaster Universities Osteoarthritis Index tested in this study

Models	Chi-square	DF	Chi-square/DF	CFI	TLI	RMSEA (90% CI)	SRMR	AIC	BIC
Model 1	415.205	249	1.66	0.869	0.854	0.057 (0.048-0.067)	0.093	8381.240	8543.587
Model 2	69.288	53	1.30	0.976	0.970	0.039 (0.000-0.063)	0.070	3807.299	3883.503
Model 3	413.064	229	1.80	0.848	0.832	0.063 (0.053-0.073)	0.097	8353.780	8522.754
Model 4	113.145	43	2.63	0.850	0.809	0.090 (0.070-0.110)	0.098	4175.547	4258.377

DF = degree of freedom; CFI = comparative fit index; TLI = Tucker-Lewis index; RMSEA = root mean square error of approximation; CI = confidence interval; SRMR: standardized root mean square residual; AIC = Akaike information criterion; BIC: Bayesian information criterion.
Model 1: two domains, four items in the pain domain and 20 items in the physical function domain; Model 2: two domains, four items in the pain domain and eight items in the physical function domain; Model 3: original version proposed by Fernandes, five items in the pain domain, two items in the stiffness domain and 17 items in the physical function domain; Model 4: version proposed by Bilbao et al., three items in the pain domain and eight items in the physical function domain.

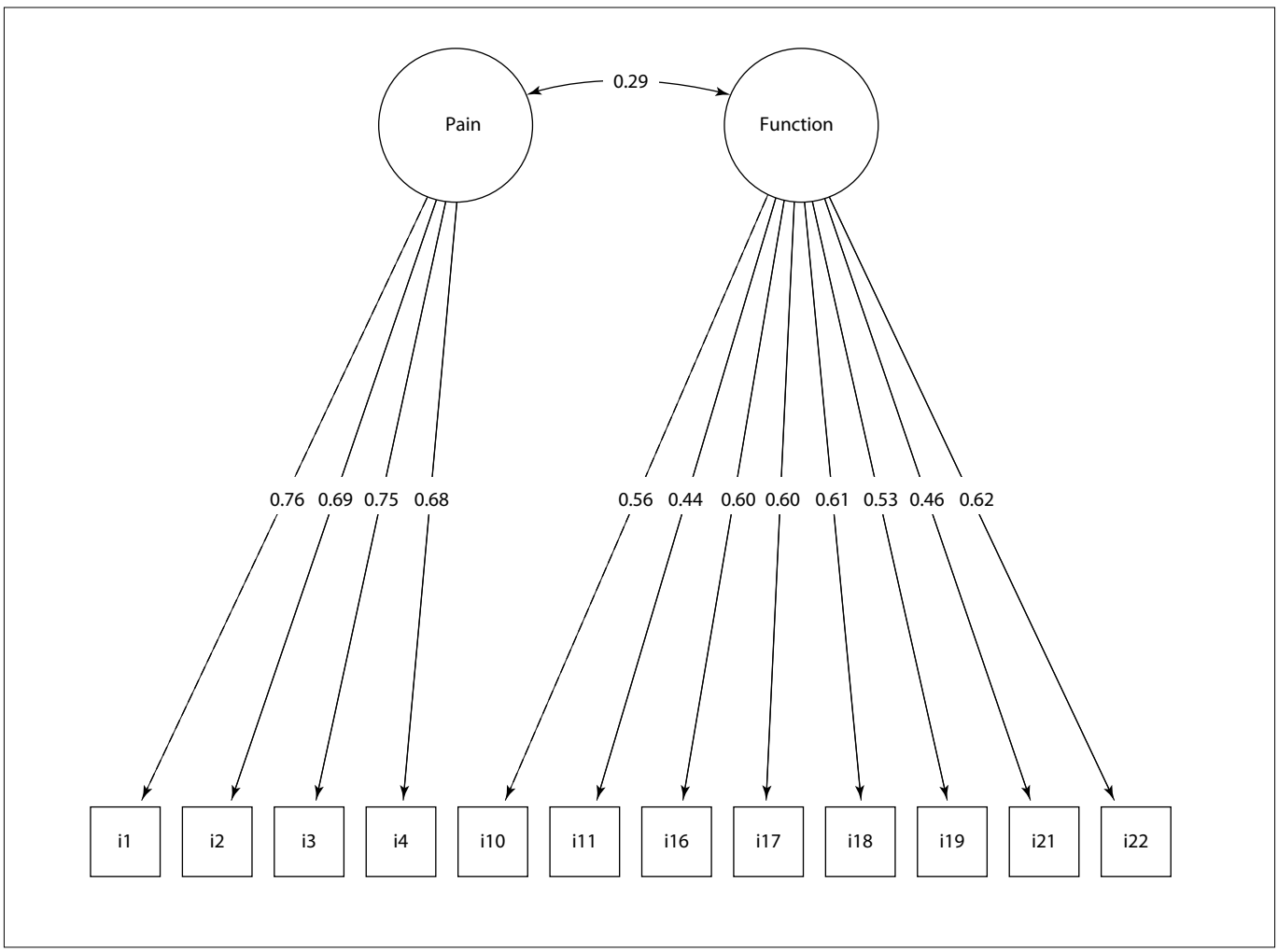

Figure 2. Domains and factorial loads of items of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Bilbao et al.[4] included patients with hip osteoarthritis and identified a Spanish WOMAC structure with two domains: pain (three items) and physical function (eight items). According to our results, the structure of WOMAC in Brazilian Portuguese also presents the same two domains. However, we identified one more item in the pain domain (item 3), and we also identified eight items in the physical function domain; but of these eight items, only three are in agreement with the aforementioned study (items 10, 16 and 22). In addition, we performed a comparison between different structures for WOMAC; the structure that we proposed presented better fit indices for the model compared with the original structure of WOMAC (three domains; 24 items) and the structure proposed by Bilbao et al.[4]

Our data show that the original version of WOMAC, traditionally used in Brazil by researchers and clinical professionals,

should be replaced by the short version presented here. WOMAC is the questionnaire most used to track and identify the signs and symptoms of patients with osteoarthritis. It is an adequate tool for following the clinical changes among patients in the light of therapeutic interventions. We firmly believe that our results, based on factor analysis and model comparison, should serve as a basis for a new understanding of WOMAC and its "pain" and "physical function" domains.

Our study has some limitations. Only structural validity was considered in the present study. Our sample consisted of patients with knee osteoarthritis, and hip osteoarthritis patients were not included. Other important psychometric properties need to be evaluated through future studies, such as reliability and construct validity (correlation with other instruments and questionnaires that measure pain and function).[9]

CONCLUSION

The Brazilian version of WOMAC with two domains, i.e. "pain" (four items) and "physical function" (eight items), presents the best structure.

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Address for correspondence:
Cid André Fidelis-de-Paula-Gomes
Programa de Pós-graduação em Ciências da Reabilitação, Universidade Nove de Julho (UNINOVE)
R. Vergueiro, 235/249 — 2º subsolo
Liberdade — São Paulo (SP) — Brasil
CEP 01504-001
Tel. (+55 11) 3385-9241
E-mail: cid.andre@gmail.com

Appendix 1. Short version of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for the Brazilian population.

DOR

As questões abaixo se referem à intensidade de dor que você geralmente sente devido à artrose. Para cada situação, por favor, marque a intensidade da dor sentida nas últimas 72 horas (marcar suas respostas com um "X").

Qual a intensidade de dor que você apresentou...

1 - Caminhando em um lugar plano?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

2 - Subindo ou descendo escadas?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

3 - Deitado(a) na cama à noite?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

4 - Sentando-se ou deitando-se?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

FUNÇÃO

As questões abaixo se referem à sua atividade física, isso quer dizer sua capacidade para movimentar-se e para cuidar-se. Para cada uma das atividades abaixo, por favor, marque o grau de dificuldade que você apresentou para realizá-las nas últimas 72 horas devido à artrose (favor marcar suas respostas com um "X").

Qual o grau de dificuldade que você apresentou ao...

10 - Levantar-se estando sentado(a)?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

11 - Ficar em pé?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

16 - Colocar as meias?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

17 - Levantar-se da cama?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

18 - Tirar as meias?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

19 - Ficar deitado(a) na cama?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

21 - Sentar-se?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

22 - Sentar-se ou levantar-se do vaso sanitário?

Nenhuma ☐ Pouca ☐ Moderada ☐ Intensa ☐ Muito Intensa ☐

Is perioperative fasting associated with complications, length of hospital stay and mortality among gastric and colorectal cancer patients? A cohort study

Isabel Pinto Amorim das Virgens[I], Ana Lúcia Miranda de Carvalho[II], Yasmim Guerreiro Nagashima[III], Flavia Moraes Silva[IV], Ana Paula Trussardi Fayh[V]

Surgical Oncology Department, Luiz Antônio Hospital, Liga Norteriograndense Contra o Câncer, Natal (RN), Brazil

[I]BSc. Dietitian and Master's student, Postgraduate Program on Health Sciences, Universidade Federal do Rio Grande do Norte (UFRN), Natal (RN), Brazil.
orcid.org/0000-0001-5563-5837

[II]MSc. Dietitian, Surgical Oncology Department, Luiz Antônio Hospital, Liga Norteriograndense Contra o Câncer, Natal (RN), Brazil.
orcid.org/0000-0002-6597-1102

[III]BSc. Dietitian, Surgical Oncology Department, Luiz Antônio Hospital, Liga Norteriograndense Contra o Câncer, Natal (RN), Brazil.
orcid.org/0000-0001-6242-6988

[IV]PhD. Dietitian and Adjunct Professor, Department of Nutrition, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre (RS), Brazil.
orcid.org/0000-0003-0730-5424

[V]PhD. Dietitian and Associated Professor, Department of Nutrition, Universidade Federal do Rio Grande do Norte (UFRN), Natal (RN), Brazil.
orcid.org/0000-0002-9130-9630

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Perioperative fasting.

ABSTRACT

BACKGROUND: During a surgical procedure, patients are often subjected to fasting for times that are more prolonged than the ideal, which may lead to complications.

OBJECTIVE: To evaluate the duration of perioperative fasting and its association with postoperative complications, length of hospital stay (LOS) and mortality among gastric and colorectal cancer patients.

DESIGN AND SETTING: Cohort study developed in a surgical oncology hospital in the city of Natal (Rio Grande do Norte, Brazil).

METHODS: Patients aged over 18 years were included. The Clavien-Dindo surgical complication scale was used to evaluate occurrences of postoperative complications. LOS was defined as the number of days for which patients stayed in the hospital after surgery, or until the day of death.

RESULTS: Seventy-seven patients participated (59.8 ± 11.8 years; 54.5% females; 70.1% with bowel tumor). The incidences of postoperative complications and death were 59.7% and 3.9%, respectively. The duration of perioperative fasting was 59.0 ± 21.4 hours, and it was higher among non-survivors and among patients with prolonged hospital stay (≥ 6 days). For each one-hour increase in the durations of perioperative and postoperative fasting, the odds of prolonged hospitalization increased by 12% (odds ratio, OR = 1.12; 95% confidence interval, CI 1.04-1.20) and 5% (OR = 1.05; 95% CI 1.02-1.08), respectively.

CONCLUSION: Prolonged perioperative fasting, especially in the postoperative period, was observed in a sample of patients with gastric and colorectal cancer, and this was an independent predictor of LOS.

INTRODUCTION

Gastrointestinal cancers, including cancers of the esophagus and stomach, colon and rectum, liver, gallbladder, pancreas, small intestine, appendix and anus, collectively represent one of the greatest public health issues, given that they lead to almost 4.5 million deaths worldwide per year.[1] Although significant progress has been made around the world, towards reducing incidence and mortality rates through improving survival, gastrointestinal cancer is rarely detected early, and the prognosis remains poor.[2]

Several types of surgery are helpful to patients with cancer, and this can be used in combination with other types of treatment. The main goal of surgery to treat cancer is to completely remove the tumor or cancerous tissue from a specific place in the body (curative surgery), and it is most effective when performed at an early stage.[3] Although nowadays surgery can be considered to be a minimally invasive procedure, it can lead to complications when performed on patients with altered nutritional status.[4] Thus, perioperative care is extremely important for successful surgical treatment.

Unfortunately, before a surgical procedure, the real duration of fasting is often more prolonged than what is prescribed. This arises for a variety of reasons relating to the hospital routine. The routine of 12 hours or nocturnal fasting is the most common protocol before elective surgery, in order to reduce complications and adverse events relating to the gastrointestinal and respiratory tract, due to the anesthesia.[5] Preoperative nocturnal fasting was instituted when anesthetic techniques were still quite rudimentary and chloroform was used. Its main objective was to avoid respiratory complications due to vomiting and aspiration of gastric contents.[6] Nowadays, shortening of fasting through use of carbohydrate beverages, such that it is started between six and

two hours before surgery, can bring benefits regarding glycemic and functional parameters.[6] It also reduces hospitalization and does not increase the aspiration risk among patients undergoing elective surgery. Thus, shortening of fasting contributes towards maintenance of nutritional status.[7]

Despite the recommendations, implementation of these protocols is still only just beginning in many countries, including Brazil. So far, a shortened perioperative fasting period for surgical cancer patients has not yet been studied.

OBJECTIVE

The objective of this study was to evaluate the duration of perioperative fasting and its association with postoperative complications, length of hospital stay (LOS) and mortality in a sample of surgical patients with gastric and colorectal cancer.

METHODS

Design, sample and ethics

This was a prospective cohort study conducted between December 2017 and December 2018, in a surgical oncology hospital in the city of Natal, RN, Brazil. The study protocol was approved by the Human Research Ethics Committee (under protocol number 2.315.013) on October 5, 2017. Gastric and colorectal cancer patients aged over 18 years who were scheduled to undergo open surgery procedures were included. The exclusion criterion was the presence of other diseases that cause a decrease in muscle mass, such as heart failure, acquired immunodeficiency syndrome, inflammatory bowel diseases, non-cancer liver diseases or tuberculosis. Patients undergoing palliative surgery (for whom only exploratory laparotomy and biopsy were performed) were also excluded because of their extensive disease verified during the surgery.

All subjects gave their written informed consent, in accordance with the Declaration of Helsinki.

Procedures

All patients with gastric and colorectal cancer who were scheduled to undergo a surgical oncological procedure during the study period was invited to participate. Before the surgical procedure, data to characterize the sample were collected from the patients' medical records and through in-person interviews: sex, age, ethnicity, presence of comorbidities (diabetes and/or hypertension) and smoking, along with information about the tumor, any neoadjuvant treatment involving chemotherapy and/or radiotherapy that had been undertaken, and the individual's functional capacity in terms of the Eastern Cooperative Oncology Group Performance Status (ECOG-PS).[8] All patients were followed up for 30 days after the surgical procedure, regardless of the length of their hospital stay, or until the time of death. After the surgery, information about the duration and type of surgery performed, and about occurrences of postoperative complications, were collected.

Body mass index (BMI, kg/m^2) was calculated from height and weight. From this, the patients were classified as underweight, normal weight, overweight or obese, in accordance with the World Health Organization (WHO) criteria.[9] Nutritional status was also evaluated by means of the Patient-Generated Subjective Global Assessment (PG-SGA). Score A indicated a patient without malnutrition, while scores B and C represented malnourishment (suggestive of moderate malnutrition and severe malnutrition, respectively).[10]

Fasting was considered to consist of absence of oral (food and drink), enteral or parenteral nutrition. Patients were asked directly what the duration of their fasting before and after surgery had been and confirmation of this was sought from the electronic records, whenever possible. Only when it was not possible to obtain reliable information regarding the duration of fasting from the patient was information from the medical records used.

Outcomes

The outcomes from this study comprised surgical complications, duration of hospitalization and incidence of hospital death. The Clavien-Dindo scale was used to evaluate surgical complications.[11] This classifies complications in ascending degrees, from I to V, according to their severity, and in our study the version of the scale translated and adapted for use in Brazilian Portuguese was used.[12] Based on other similar studies in the literature,[13-15] only complications classified as grade II onwards were considered in the present study. Grade II complications include infectious processes treated with antibiotics, need for blood transfusion and parenteral nutrition. Complications of grades III, IV and V include surgical re-interventions for correction of fistulas, intra-abdominal abscess and evisceration, intensive care unit (ICU) hospitalizations for treatment of abdominal sepsis, and death. The LOS was defined as the number of days for which patients stayed at the hospital after surgery, or until the day of death.

Statistical analysis

Descriptive statistics were calculated and the data were expressed as the mean and standard deviation for quantitative parametric variables; as the median and interquartile range (P25-P75) for quantitative nonparametric variables; or as the absolute and relative frequency for categorical variables. The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test. Clinical and nutritional characteristics were compared between groups using the chi-square test for categorical variables and using the independent t test

(parametric variables) or Mann-Whitney test (nonparametric variables) for continuous variables. Correlations between the duration of fasting and the length of hospital stay after surgery were evaluated using Spearman's coefficient.

Logistic regression was performed considering the length of hospital stay (categorized according to the median of six days), incidence of postoperative complications and death in hospital as dependent variables; and the duration of perioperative or postoperative fasting as independent variables. The covariates included in the adjusted model were the patients' ages, nutritional status according to PG-SGA, tumor site and stage, duration of postoperative hospital stay and occurrence of complications in the postoperative period. The durations of perioperative or postoperative fasting were considered to be continuous variables in the model constructed. All the analyses were performed in the SPSS 20.0 software and P-values < 0.05 were considered statistically significant.

RESULTS

A total of 140 patients were initially screened before surgery, but 63 of them were excluded because their data regarding the duration of pre or postoperative fasting were incomplete. Therefore, 77 patients of mean age 59.8 ± 11.8 years were enrolled in this study. **Table 1** describes the baseline demographic characteristics of the sample.

The mean duration of preoperative fasting was 15.9 ± 5.3 hours, while the median duration of postoperative fasting was 39.9 (19.5-46.9) hours. The duration of perioperative fasting was 59.0 ± 21.4 hours. Death occurred in the case of three individuals, of whom two were colorectal cancer patients. **Table 2** shows the patients' clinical and nutritional features according to the cancer site. In general, gastric cancer patients had worse status performance and presented longer duration of surgery and more complications than did colorectal cancer patients. Also, LOS was greater among gastric cancer patients. Although the surgical complications differed between the groups, the time taken (in days) for complications to appear was not different.

The duration of fasting did not differ between patients with and without complications in the postoperative period, as demonstrated in **Table 3**. Survivors had shorter postoperative and perioperative fasting, in comparison with non-survivors. Patients with longer hospitalization after surgery had longer durations of fasting during the postoperative and perioperative period than patients with hospital stays after surgery shorter than six days.

Logistic regression was performed to evaluate the association between prolonged hospitalization after surgery (≥ 6 days) and the duration of perioperative or postoperative fasting (**Table 4**). For each one-hour increase in the duration of perioperative fasting, the odds of prolonged hospitalization increased by 12%; while for each one-hour increase in the duration of postoperative fasting, it increased by 5%. In the multivariate analysis adjusted for confounders, the duration of perioperative or postoperative fasting was not an independent predictor of postoperative complications or death in the hospital. A one-hour increase in the durations of postoperative and perioperative fasting increased the odds of death by 14% and 15%, respectively, but it did not reach statistical significance after adjustment for confounders.

Table 1. Clinical and nutritional features of the surgical patients (n = 77)

Variables	n	%
Gender (%)		
Female	42	54.5
Ethnicity (%)		
Non-Caucasian	58	75.3
Hypertension (%)		
Yes	45	58.4
Diabetic (%)		
Yes	17	22.1
Smoking history (%)		
Yes	28	36.4
Alcohol consumption (%)		
Yes	26	33.8
Tumor site (%)		
Gastric	23	29.9
Colorectal	54	70.1
Clinical tumor stage		
I	17	22.1
II	17	22.1
III	22	28.6
IV	14	18.2
Unknown	7	9.1
Neoadjuvant treatment		
Yes	29	37.7
BMI classification		
Undernutrition	4	5.2
Normal weight	31	40.3
Overweight	32	41.6
Obesity	10	13.0
PG-SGA classification		
A	49	63.6
B or C	28	36.4
ECOG-PS		
0	36	46.8
1	29	37.7
2	9	11.7
3	2	2.6
4	1	1.3
Complications		
Yes	46	59.7

BMI = body index mass; PG-SGA = Patient-Generated Subjective Global Assessment; ECOG-PS = Eastern Cooperative Oncology Group Performance Status.

DISCUSSION

The aim of the current study was to evaluate the duration of perioperative fasting and its association with postoperative complications, LOS and mortality in a sample of surgical patients with gastric and colorectal cancer. The mean duration of perioperative fasting was long (59 hours). Although fasting was not associated with the incidence of postoperative complications and death, a one-hour increase in perioperative fasting was associated with

Table 2. Comparison between clinical and nutritional characteristics according to cancer site

	Total (n = 77)	Gastric cancer (n = 23)	Colorectal cancer (n = 54)	P
Undernutrition[1]	28 (36.4%)	10 (43.5%)	18 (33.3%)	0.397*
Excess weight[2]	42 (54.5%)	13 (56.5%)	29 (53.7%)	0.820*
Good performance status[3]	65 (84.4%)	16 (69.6%)	49 (90.7%)	0.019*
Clinical tumor stages III and IV	39 (50.6%)	13 (56.5%)	23 (42.6%)	0.083*
With surgical complications	46 (59.7%)	18 (78.3%)	28 (51.9%)	0.031*
Preoperative fasting (h)	15.90 ± 5.31	15.29 ± 3.81	16.16 ± 5.85	0.514#
Postoperative fasting (h)	39.92 (19.54-46.96)	41.00 (19.08-63.33)	39.87 (16.62-46.50)	0.501π
Perioperative fasting (h)	58.95 ± 21.45	61.96 ± 26.91	57.67 ± 18.79	0.425#
Duration of surgery (min)	183.75 ± 68.36	215.4 ± 73.6	170.3 ± 61.9	0.007#
Length of hospital stay (days)	6.0 (4.0-8.0)	8.0 (7.0-12.0)	5.0 (4.0-7.0)	< 0.001π
Number of days taken for complications to appear	3.0 (2.0-8.0)	4.0 (1.8-7.0)	3.0 (2.0-11.0)	0.847π

[1]According to the Patient-Generated Subjective Global Assessment (PG-SGA); [2]According to body mass index ≥ 25 kg/m^2; [3]Eastern Cooperative Oncology Group Performance Status ≤ 1; *P-value with chi-square test; #P-value with independent t test πP-value with Mann-Whitney test.

Table 3. Duration of perioperative fasting among patients with gastric and colorectal cancer according to survival, incidence of complications and length of hospital stay (LOS) after surgery

	Survivors (n = 74)	Non-survivors (n = 3)	P
Preoperative fasting (h)	15.9 ± 5.4	16.2 ± 5.2	0.956[1]
Postoperative fasting (h)	39.2 (19.1 - 46.7)	77.4 (16.9-65.5)	0.038[2]
Perioperative fasting (h)	57.9 ± 20.6	97.0 ± 21.2	0.010[1]
	Without complications (n = 31)	**With complications(n = 46)**	**P**
Preoperative fasting (h)	16.0 ± 6.9	15.9 ± 4.0	0.728[1]
Postoperative fasting (h)	39.2 (17.5-49.1)	40.9 (21.0-46.5)	0.175[2]
Perioperative fasting (h)	57.9 ± 20.5	59.7 ± 22.3	0.917[1]
	LOS after surgery < 6 days (n = 35)	**LOS after surgery ≥ 6 days (n = 42)**	**P**
Preoperative fasting (h)	17.4 ± 6.1	14.7 ± 4.3	0.001[1]
Postoperative fasting (h)	36.3 (16.5-41.3)	45.0 (33.4-69.8)	0.001[2]
Perioperative fasting (h)	50.4 ± 14.5	66.1 ± 23.8	< 0.001[1]

[1]Student t test (data presented as mean ± standard deviation); [2]Mann-Whitney test [data presented as median (P25-P75)].

Table 4. Association between fasting and clinical outcomes, from multivariate analyses

	Mortality OR (95% CI)	P
Postoperative fasting (h)[1]	1.04 (0.99-1.09)	0.069
Postoperative fasting (h)[2]	1.14 (0.99-1.31)	0.065
Perioperative fasting (h)[1]	1.05 (1.00-1.10)	0.044
Perioperative fasting (h)[2]	1.15 (0.99-1.34)	0.071
	Postoperative complications OR (95% CI)	**P**
Postoperative fasting (h)[1]	1.00 (0.96-1.05)	0.967
Postoperative fasting (h)[3]	0.96 (0.92-1.01)	0.099
	Prolonged hospitalization (length of hospital stay after surgery > 6 days) OR (95% CI)	**P**
Postoperative fasting (h)[1]	1.05 (1.02-1.07)	0.001
Postoperative fasting (h)[4]	1.01 (1.04-1.17)	0.002
Perioperative fasting (h)[1]	1.05 (1.02-1.08)	0.002
Perioperative fasting (h)[4]	1.12 (1.04-1.20)	0.002

Logistic regression. OR = odds ratio; 95% CI = 95% confidence interval.
[1]Crude model; [2]model adjusted for age, nutritional status according to PG-SGA, tumor site and occurrence of complications in postoperative period; [3]model adjusted for age, nutritional status according to PG-SGA, tumor site, tumor stage and length of postoperative hospitalization; [4]model adjusted for age, nutritional status according to PG-SGA, tumor site, tumor stage and occurrence of complications in postoperative period.

an increase of 12% in the odds of prolonged hospitalization after surgery. To date, no other study on cancer patients has evaluated the impact of perioperative fasting on selected outcomes (postoperative complications, LOS and death).

Nutritional care for cancer patients undergoing surgery extends well beyond the perioperative period. The adverse effects of prolonged fasting on glucose metabolism have already been reported,[16-18] but the effects relating to postoperative complications remain unclear. Conventionally, feeding for patients undergoing gastrointestinal surgeries has been prescribed only after the return of peristalsis, clinically characterized by the appearance of bowel sounds and elimination of flatus.[19] However, nowadays, experts are contesting this type of conduct, because evidence has shown that early feeding can be administered with minimal risks and with potential benefits for patients.[20] The same has been described in relation to preoperative fasting, and there is a consensus in the literature regarding the importance of keeping this short. This is extremely important in populations such as that of the present study, with high frequency of diabetes (22%) and overweight (54.6%), as these individuals present the characteristics of oxidative stress and inflammation.

The mean duration of preoperative fasting was approximately 16 hours. This was longer than recommended, even in conservative prescriptions, but was in line with what had been reported in other studies without any implementation of measures to shorten the fasting protocol. Pereira et al. observed that the average duration of preoperative fasting in a sample of 128 surgical cancer patients was 26.4 ± 47.1 hours, but the average total length of fasting was 107.6 ± 73 hours.[21] Falconer et al. interviewed 292 surgical patients, of whom 192 (65.8%) had undergone elective operations. All of the elective patients had received instructions for preoperative fasting of duration longer than six hours.[20] The results showed that the mean duration of preoperative fasting from solids was 13.5 hours (interquartile range, IQR 11.5-16 hours). A variety of clinical factors may require prolonged preoperative fasting, such as for patients with a high risk of aspiration and those with medical conditions that may delay gastric emptying.[20] Aguilar-Nascimento et al. believed that both clinicians and patients might still believe that fasting from midnight onwards was safer.[22]

Although the duration of perioperative fasting was considered high, it was not associated with complications in the postoperative period. To the best of our knowledge, this study was the first to describe this relationship, and probably the prolonged fasting was not due to the patients' conditions, but to those of the healthcare establishment, such as the availability of the surgical center and the medical staff. Despite preoperative nutritional care, patients remain at risk of postoperative complications and deterioration of nutritional status.[7]

The results from the present study also show that non-survivor patients experienced a more prolonged duration of post and perioperative fasting. In the multivariate analysis, the durations of postoperative and perioperative fasting were probably not independent factors for mortality due to a lack of study power, given that the incidence of death was low in the current study. There is also a dearth of prospective studies about perioperative fasting focusing on selected outcomes (complications and mortality) among patients undergoing major surgery for cancer.

Receiving nothing orally for a long time preoperatively constitutes a persistent intervention and results in discomfort among patients. Clinical protocols should therefore be revised.[23] In a case study,[24] three patients were followed before and after laparoscopic colorectal resection: one with control fasting, another with shortened preoperative fasting and the third with shortened pre and postoperative fasting. Even with the shortened protocol, the latter two patients underwent preoperative fasting for approximately 17 hours, while the control patient remained in a fasting state for 43 hours. Additionally, the control patient showed increasing preoperative discomfort (hunger, thirst and anxiety), compared with the other two patients. However, the mean duration of hospital stay was not statistically significant different.[24]

Another interesting finding from the present study was that there was an association between the duration of perioperative fasting and prolonged hospitalization after surgery. A one-hour increase in the duration of perioperative fasting increased the odds of prolonged hospitalization by 12%; while a one-hour increase in the duration of postoperative fasting increased the odds of this outcome by 5%. An interesting study described the duration of preoperative fasting at a single center among surgical cancer patients before and after implementation of the enhanced recovery after surgery (ERAS) protocol.[19] With the implementation of this protocol, the authors observed a significant decrease in the duration of preoperative fasting (14.7 [4-48] hours versus 7.2 [1-48] hours), but without any difference in the length of postoperative hospital stay (3.9 [0-51] versus 3.2 [0-15] days; P = 0.52). This was similar to the results from the present study, i.e. among patients whose duration of preoperative fasting was up to five hours, the length of hospitalization decreased by one day (3.8 [0-51] versus 2.5 [0-15] days). Our results show the importance of reducing the durations of both pre and postoperative fasting.

Although several studies in the literature have shown that implementation of a shortening of the fasting protocol in surgical cases entailed shorter hospitalization and improved postoperative recovery, data from cancer patients are scarce. Pereira et al. evaluated 128 patients who underwent surgical treatment for gastrointestinal cancer.[21] The total length of fasting (mean of 107.6 hours) was significantly associated with the number of symptoms presented before and after the surgery. Differently from the

present study, those authors did not evaluate surgical complications in accordance with the Clavien-Dindo scale. In a systematic review on shortening of fasting among patients undergoing oncological surgery, Pinto et al. analyzed four studies with a total of 150 patients (128 with colorectal cancer and 22 with gastric cancer).[25] In comparison with traditional protocols, patients undergoing shortening of fasting through administration of fluids containing carbohydrates showed improvements in glycemic and inflammatory parameters and in malnutrition indicators, along with shorter hospital stay.

This study has several limitations. First, the data collection method may have been a source of information bias since there is an element of subjectivity inherent in patient recall. It was also not possible to identify whether the fasting related only to medical prescription or whether the patients were unable to tolerate oral food, which probably related to the length of hospital stay. Second, the study was conducted in a single center and included patients with different cancer sites (heterogeneity of the study subjects and surgical procedures used). However, the baseline characteristics were not significantly different between the groups. Furthermore, the incidence of death in this sample was low, and it prevented us from performing multivariate analysis adjusted for confounders, in order to investigate the real association between perioperative fasting and mortality. In addition, the study was conducted using a convenience sample and the analysis should be considered exploratory since the power of the study to test the hypothesis was not predefined. This matter needs to be better explored in further studies with larger samples.

CONCLUSION

Prolonged perioperative fasting was observed in this sample of patients with gastric and colorectal cancer and it was an independent predictor of the length of hospital stay. This result emphasizes that there is a need for protocols to shorten fasting in this group of patients.

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Address for correspondence:
Ana Paula Trussardi Fayh
Departamento de Nutrição, Centro de Ciências da Saúde, Universidade Federal do Rio Grande do Norte (UFRN)
Av. Senador Salgado Filho, 3.000
Natal (RN) — Brasil
CEP 59078-970
Tel. (+55 84) 99426-3363
E-mail: apfayh@yahoo.com.br

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The effect of prophylactic rewarming on postoperative nausea and vomiting among patients undergoing laparoscopic hysterectomy: a prospective randomized clinical study

DongDong Liang[I], YuanLu Shan[II], Leilei Wang[III]

Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Area, Wenzhou City, Zhejiang Province, China

[I]MD. Anesthesiologist, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Area, Wenzhou City, Zhejiang Province, China.
orcid.org/0000-0002-7275-1845

[II]MD. Anesthesiologist, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Area, Wenzhou City, Zhejiang Province, China.
orcid.org/0000-0002-5600-5543

[III]MD. Anesthesiologist, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Area, Wenzhou City, Zhejiang Province, China.
orcid.org/0000-0002-3660-2594

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ABSTRACT

BACKGROUND: Postoperative nausea and vomiting (PONV) is a common complication from general anesthesia that impacts on postoperative recovery.

OBJECTIVE: To evaluate prophylactic rewarming following general anesthesia, so as to decrease the incidence of PONV among patients undergoing laparoscopic hysterectomy.

DESIGN AND SETTING: Prospective randomized clinical study at a hospital in China.

METHODS: Sixty-two patients were randomly assigned into two groups. The forced air warming (FAW) group received pre-warmed Ringer's solution with FAW until the end of surgery. The control group received Ringer's solution without FAW. The pre-warmed Ringer's solution was stored in a cabinet set at 40 °C. The FAW tube was placed beside the patient's shoulder with a temperature of 43 °C.

RESULTS: Sixty patients completed the study. The FAW group showed significant differences versus the controls regarding temperature. At 6, 24 and 48 hours postoperatively, the incidences of PONV were 53.3%, 6.7% and 3.3% in the FAW group versus 63.3%, 30% and 3.3% in the controls. VAS scores were significantly lower in the FAW group than in the controls at 24 hours (P= 0.035). Forty-item questionnaire total scores in the FAW group were significantly higher than in the controls. The physical independence and pain scores at 24 hours and emotional support and pain scores at 48 hours in the FAW group were higher than in the controls ($P < 0.05$). There was no difference in hemodynamics or demographics between the two groups ($P > 0.05$).

CONCLUSIONS: Prophylactic rewarming relieved PONV and improved the quality of postoperative recovery.

CHINESE CLINICAL TRIAL REGISTER (CHICTR): ChiCTR-IOR-17012901.

INTRODUCTION

Postoperative nausea and vomiting (PONV) after general anesthesia has high incidence (20%-80%). It is an uncomfortable complication that causes distress for patients.[1] It occurs much more frequently among high-risk patients (60-70%), such as females, individuals who suffer from motion sickness, nonsmokers and individuals with a history of PONV.[2] Laparoscopic surgery is prone to induce postoperative nausea and vomiting, which significantly increases patients' discomfort, such that they hardly take in any nutritious food, which thus results in extending their length of hospital stay.[3] Multiple antiemetic drugs have been applied in clinics, but the efficacy of such treatment comes with risks of adverse events such as excessive sedation,[4] dizziness, dry mouth, dysphoria, mood changes,[5] tachycardia and extrapyramidal signs.

Besides drug therapy, nondrug therapy also provides some help in preventing occurrences of PONV. Intraoperative skin surface rewarming is a common and rapid method that not only can prevent hypothermia but also can improve postoperative comfort.[6,7] Rein et al.[8] and Hamza et al.[9] showed that perioperative temperature protection increased skin blood flow and heat transfer, and also lowered the requirement for analgesics and promoted higher quality of recovery.[10] Reflective blankets,[11] forced-air warmers and warm socks have all been used clinically to prevent shivering and maintain subjective thermal comfort postoperatively,[12,13] thereby indirectly minimizing development of PONV.

The underlying mechanisms of PONV are complex and relate to the patient's psychological state. Watcha and White believed that vagal stimuli from the intestinal tract could activate the emetic center and trigger chemoreceptors, which would result in a series of reactions to the onset

of nausea and vomiting.[4] Some clinical trials have shown that oral administration of warm water for four hours postoperatively had the capacity to significantly decrease the first flatus expulsion, relieve gastrointestinal spasms and help peristalsis return at an early stage of recovery.[14]

Therefore, we hypothesized that thermal protection for patients would prevent PONV and provide better benefit in recovery. To test this hypothesis, we applied forced-air warmers combined with warm liquid to maintain temperature fluctuation perioperatively; a 100-mm visual analogue scale (VAS) to evaluate overall postoperative PONV; and a 40-item questionnaire (QoR-40) to measure the quality of recovery.

OBJECTIVE

The aim of this study was to evaluate prophylactic rewarming following general anesthesia, to guard against postoperative nausea and vomiting among patients undergoing laparoscopic hysterectomy.

METHODS

The present study was registered in the Chinese Clinical Trial Register with the code ChiCTR-IOR-17012901. This was a prospective randomized study in which 62 patients who were candidates for laparoscopic hysterectomy under general anesthesia at a hospital in China were enrolled between July 2017 and March 2018. In accordance with the requirements of the ethics committee for clinical research (number 2017-162), the patients were given explanations about the purpose of the study protocol and they gave their written consent to participate. The clinical trial consent and QoR-40 questionnaire were explained to the patients one day before surgery.

From the surgical list, we identified the patients who were eligible to become involved in the clinical trial. Patients who conformed to the inclusion criteria were allocated before the surgery either to the forced air warming (FAW) group or to the control group by means of numbers in identical sealed envelopes, according to a random number table that was created through a computer by an independent statistician. One of the anesthesiologists (WLL) made an evaluation and recorded the data after the participants had signed the consent form.

An independent nurse who was not involved in caring for these patients opened the envelopes before the operation and prepared the fluids and FAW. The FAW tube was placed beside the patient's shoulder with the temperature at 43 °C. Two of the anesthesiologists (LDD, SYL), who were unaware of the allocation group, performed the general anesthesia and all intraoperative data recording, and another investigator (WLL) was in charge of all postoperative assessments, while blinded to the group identity.

Subjects

The inclusion criteria were that the subjects needed to present the following: American Society of Anesthesiologists (ASA) physical status I/II; aged 20 to 60 years; consent to their participation in the study until the end; scheduled to undergo laparoscopic hysterectomy. Written informed consent was obtained from all subjects. All of them answered the QoR-40 questionnaire independently.

Presentation of any of the following were deemed to be exclusion criteria: allergy; bronchial asthma; coronary heart disease; obesity-related diabetes mellitus; hypertension; BMI > 30 kg/m^2; cardiac, hepatic or renal dysfunction; psychiatric disease; chronic pain; fever; history of alcohol or opioid abuse; intake of any nonsteroidal analgesics or antiepileptic drugs within 48 hours before surgery; or history of gastrointestinal disease (peptic ulcer, Crohn's disease or ulcerative colitis). Patients were withdrawn from the groups if their laparoscopy was converted to open surgery.

Sixty female patients aged 20 to 60 years who presented ASA physical status I or II and had been scheduled for primary gynecological laparoscopic surgery were randomly assigned to two groups. Patients in the FAW group received pre-warmed Ringer's solution that was stored in a heating cabinet set at 40 °C and was applied with forced air warming (FAW) that was switched on until the end of surgery. Patients in the control group received normal general anesthesia with normal Ringer's solution, i.e. FAW was switched off. To ensure that the surgery went smoothly, we set the patients' intraoperative temperature to be not lower than 35 °C. In the event of lower temperatures occurring in the control group, our intention was to stop the trial and take protective measures.

Anesthesia was induced in all patients by means of propofol 2 (mg/kg) and sufentanil (0.3-0.5 μg/kg), and intubation was done using cisatracurium (2 mg/kg). Anesthesia was maintained by means of sevoflurane, propofol and remifentanil. The bispectral index (BIS) was monitored to maintain it at 45-55 in order to control the infusion speed of anesthetic drugs.

Mechanical ventilation was performed to maintain $PetCO_2$ at 35-40 mmHg. Sufentanil (0.1 mg/kg per 30 minutes) was administered during the surgery to provide analgesia. Intravenous ondansetron (8 mg) was administered to prevent postoperative nausea and vomiting. When patients presented spontaneous breathing, consciousness was recovered by using neostigmine and atropine, and then the tracheal tube was extracted.

Measurement

1. Postoperative nausea and vomiting were evaluated and measured by means of a 100-mm VAS at the postoperative time points of 6 hours, 24 hours and 48 hours. Additionally, we recorded any occurrences of nausea and vomiting in the ward, and the number of times of using antiemetic drugs.

2. Core temperature was recorded by using a temperature probe placed in the nasal cavity. We set 37.0 °C as the starting temperature in both groups. The changes in nasal temperature were recorded as follows: ΔT_0 (ΔT_0 = 37.0 °C – the intubation temperature); ΔT_{30} (ΔT_{30} = intubation temperature – temperature 30 minutes after intubation), ΔT_{60} (ΔT_{60} = intubation temperature – temperature 60 minutes after intubation), ΔT_{90} (ΔT_{90} = intubation temperature – temperature 90 minutes after intubation).
3. The validated Chinese version of the QoR-40 questionnaire was used at three times: preoperatively (T0), 24 hours postoperatively (T1) and 48 hours postoperatively (T2).[15,16] QoR-40 contains five subscales: physical comfort (PC), emotional state (ES), physical independence (PI), patient support (PS) and pain (P). Each item is rated on a scale of 1-5, and therefore the total score can range from a minimum of 40 to a maximum of 200. The QoR-40 questionnaire was used to measure the patients' physical condition after anesthesia.
4. Perioperative hemodynamics: heart rate and mean arterial pressure (MAP) were recorded at the times of the baseline, intubation and 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes and 60 minutes after induction of anesthesia, and at the end of surgery.
5. Occurrences of shivering[17] (at the end of surgery and in the early postoperative period up to one hour) were evaluated and recorded in two groups, as follows:
   - grade 1: no shivering
   - grade 2: mild shivering, with slight facial and cervical muscle contraction
   - grade 3: moderate shivering, consisting of obvious shivering of the head and neck, shoulders, and/or extremities
   - grade 4: severe shivering, consisting of obvious shaking all over the body
6. The patients' demographic profiles in the two groups were recorded, including age, body mass index, intraoperative sufentanil and remifentanil consumption, liquid dosage, time of extubation and durations of anesthesia and the operation.

Data analysis and statistics

The demographic profiles were analyzed by means of the independent-sample t test. The paired-sample t test was used to test for significant differences in ΔT between the two groups. The Wilcoxon test with the Mann-Whitney U test was used to analyze PONV scores and QoR-40 scores. Repeated-measurement analysis of variance (ANOVA) followed by the Huynh-Feld correction was used for analysis on MAP and heart rate. Occurrences of shivering were tested using the chi-square test with Fisher's exact test.

All values were presented as means ± standard deviation (SD). All the analyses were performed using the SPSS statistical software (SPSS Inc., Chicago, Illinois, USA). P-values < 0.05 were considered statistically significant.

RESULTS

1. Postoperative nausea and vomiting:

At 6 hours after the operation, the incidences of PONV were 53.3% (16/30) in the FAW group and 63.3% (19/30) in the control group, within which the vomiting rates were 20% (6/30) in the FAW group and 23.3% (7/30) in the control group. However, there was no statistically significant in VAS scores (P = 0.258). At 24 hours after the operation, the incidences of PONV were 6.7% (2/30) in the FAW group and 30% (9/30) in the control group, within which the vomiting rates in the two groups were equal, at 3.3% (1/30). The VAS scores in the control group were significantly higher than those in the FAW group (P = 0.035). At 48 hours after the operation, the incidences of PONV in the two groups were equal at 3.3% (1/30), and none of the subjects presented vomiting. There was no significant difference in VAS scores at 48 hours after the operation between the two groups (P = 0.981; **Table 1**).

Additionally, the proportions of the patients who presented a need for use of antiemetic drugs to relieve PONV in the ward were 46.7% (14/30) in the FAW group and 56.7% (17/30) in the control group. Ondansetron (44.3%), promethazine (1.7%) and metoclopramide (6.7%) were administered to prevent and treat nausea and vomiting in the ward.

2. Core temperature:

Starting from the baseline of intubation, there was no difference in temperature drop between the two groups. At the time of 30 minutes after intubation, there was a statistical difference in the degree of temperature decline between the two groups (FAW: ΔT_{30} = 0.0467 ± 0.12243; control: ΔT_{30} = 0.1433 ± 0.16955; P = 0.013). At the time of 60 minutes after intubation,

Table 1. Postoperative nausea and vomiting according to visual analogue scale scores in the two groups

Time	Visual analogue scale score		
	FAW group n = 30	Control group n = 30	P[α]
6 hours	2.53 ± 2.75	3.47 ± 3.13	0.258
24 hours	0.47 ± 1.78	1.00 ± 1.64	0.035*
48 hours	0.07 ± 0.37	0.10 ± 0.55	0.981

6 hours, 6 hours after operation; 24 hours, 24 hours after operation; 48 hours, 48 hours after operation; [α]obtained through the Wilcoxon test with Mann-Whitney U test; visual analogue scale scores at 24 hours after operation, FAW group (*P = 0.035) versus control group; FAW = forced air warming.

the degree of temperature decline in the FAW group was reduced. However, in the control group, the degree of temperature decline did not reduce, thus leading to a significant difference between the two groups (FAW: ΔT_{60} = 0.1367 ± 0.22664; control: ΔT_{60} = 0.3367 ± 0.20083; P = 0.001). At the time of 90 minutes after intubation, the degree of temperature decline in the FAW group was significantly reduced, compared with the control group (FAW: ΔT_{90} = 0.1400 ± 0.22834; control: ΔT_{90} = 0.3833 ± 0.24507; P = 0.000; **Figure 1**).

3. Results from QoR-40:

All the patients (n = 30 in each group) received the QoR-40 questionnaire at three times: before the operation (T0), 24 hours after the operation (T1) and 48 hours after the operation (T2). At T1, the patients in the control group had lower overall QoR-40 scores than the patients in the FAW group (P = 0.027) and lower scores for the PI and P dimensions (P = 0.032, P = 0.034 respectively). At T2, the overall QoR-40 scores in the two groups were higher and returning towards the preoperative level. Patients in the FAW group showed better recovery than those in the control group, with a statistically significant difference (P = 0.006). The ES and P dimensions in the control group had lower scores than those of the T group (P = 0.024 and P = 0.002, respectively; **Table 2**).

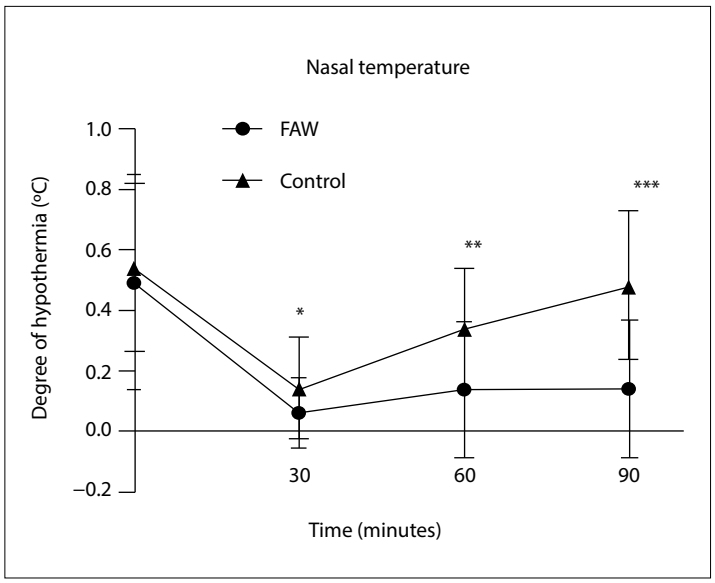

Figure 1. Changes to nasal temperature in the two groups. X axis encompasses the baseline of intubation and intubation after 30 minutes, 60 minutes and 90 minutes. Y axis represents the magnitude of the decline in temperature during the operation. All values are presented as means ± standard deviation (SD). Forced air warming (FAW) group versus control group at ΔT30 *P = 0.013, at ΔT60 **P = 0.001 and at ΔT90 ***P = 0.000, respectively.

Table 2. QoR-40 scores at T0, T1 and T2 among the patients

	FAW group n = 30	Control group n = 30	P[α]
T0			
Overall	195.73 ± 5.41	196.67 ± 4.25	0.556
Physical comfort (PC)	59.00 ± 1.53	58.97 ± 1.50	0.91
Emotional state (ES)	43.07 ± 2.96	43.10 ± 3.53	0.658
Physical independence (PI)	24.80 ± 0.76	24.87 ± 0.73	0.321
Psychological support (PS)	34.80 ± 0.48	34.77 ± 0.43	0.573
Pain (P)	34.10 ± 1.32	34.10 ± 1.185	0.877
T1			
Overall	175.50 ± 9.63	170.47 ± 9.35	0.027*
Physical comfort (PC)	50.77 ± 5.46	49.43 ± 4.75	0.233
Emotional state (ES)	42.07 ± 3.48	41.27 ± 3.62	0.11
Physical independence (PI)	17.27 ± 2.26	15.77 ± 2.53	0.032*
Psychological support (PS)	34.57 ± 0.73	34.67 ± 0.48	0.857
Pain (P)	30.90 ± 2.19	29.40 ± 2.92	0.034*
T2			
Overall	190.20 ± 5.37	186.07 ± 6.50	0.006#
Physical comfort (PC)	58.137 ± 2.21	57.70 ± 2.61	0.353
Emotional state (ES)	43.80 ± 2.04	41.83 ± 6.09	0.024*
Physical independence (PI)	20.20 ± 2.57	19.60 ± 2.76	0.18
Psychological support (PS)	34.90 ± 0.31	34.90 ± 0.31	1
Pain (P)	33.17 ± 1.56	31.33 ± 2.54	0.002#

Values are expressed as mean ± standard deviation (SD) or number of patients. T0, before surgery; T1, 24 hours after surgery; T2, 48 hours after surgery; FAW group, forced air warming group; [α]obtained through the Wilcoxon test with Mann-Whitney U test; *P < 0.05; #P < 0.01. At T1 and T2, overall scores in FAW group (*P = 0.027 and #P = 0.006, respectively) versus control group. At T1, PI and P scores in FAW group (*P = 0.032 and #P = 0.034, respectively) versus control group. At T2, ES and P scores in FAW group (*P = 0.024 and #P = 0.002, respectively) versus control group.

4. Perioperative hemodynamics:

No significant differences were seen between the two groups in terms of the perioperative MAP and heart rate (HR) (FAW: MAP = 84.4000 ± 11.36555; control: MAP = 81.7233 ± 12.21111; P > 0.05; FAW: HR = 66.0844 ± 10.06888; control: HR = 64.9811 ± 9.96222; P > 0.05; **Figure 2**). Both MAP and heart rate values decreased at the time of tracheal cannulation and then maintained a lower level than the baseline. However, these values tended to remain within an acceptable range once surgery had commenced.

5. Occurrence of shivering:

Occurrences of shivering were associated with high incidence of low temperature, compared with the control group (P = 0.024; **Table 3**).

6. Patient characteristics:

Sixty-two patients who were candidates for laparoscopic hysterectomy under general anesthesia were enrolled for this study. Two patients were excluded as a result of factors such as changes to the surgical procedure and blood sample loss. Thus, 60 female patients were included between July 2017 to March 2018, and were divided into two groups (FAW and control). There were no significant differences between the groups regarding age, body mass index, intraoperative sufentanil (34.80 ± 5.85 μg versus 35.53 ± 6.54 μg) and remifentanil consumption (679.00 ± 256.72 μg versus 728.27 ± 270.34 μg), liquid dosage (1033.33 ± 224.89 ml versus 1000.00 ± 227.43 ml), time of extubation, and durations of anesthesia and the operation (P > 0.05; **Table 4**).

Table 3. Occurrences of shivering

Group	Occurrences of shivering	
	Yes (n = 30)	No (n = 30)
FAW group	0	30
Control group	6	24
Pα	0.024*	

Values are expressed as numbers of patients.

[α]obtained through the chi-square test + Fisher's exact test. Occurrences of shivering in the FAW group (*P < 0.05) versus control group. FAW, forced air warming.

DISCUSSION

PONV is a commonly encountered symptom among patients in a variety of clinical settings.[18] PONV causes distress for patients and affects postoperative recovery quality, although the precise mechanism is still unclear. The main finding in our study was that prophylactic rewarming (pre-warmed Ringer's solution with FAW) could effectively ameliorate the condition of PONV at 24 hours after the operation. It also helped to improve the quality of early recovery among these laparoscopic hysterectomy patients, 24 hours and 48 hours after the operation.

Perioperative hypothermia has been found to tend to induce occurrence of nausea and vomiting, in many studies.[19-21] In our study, temperature values in both groups decreased markedly after intubation. However, the degree of temperature decline in the FAW group was reduced, compared with the control group, from the time of 30 minutes after intubation to the time of 90 minutes after intubation. The results suggested that pre-warming fluids applied in association with FAW were able to provide steady

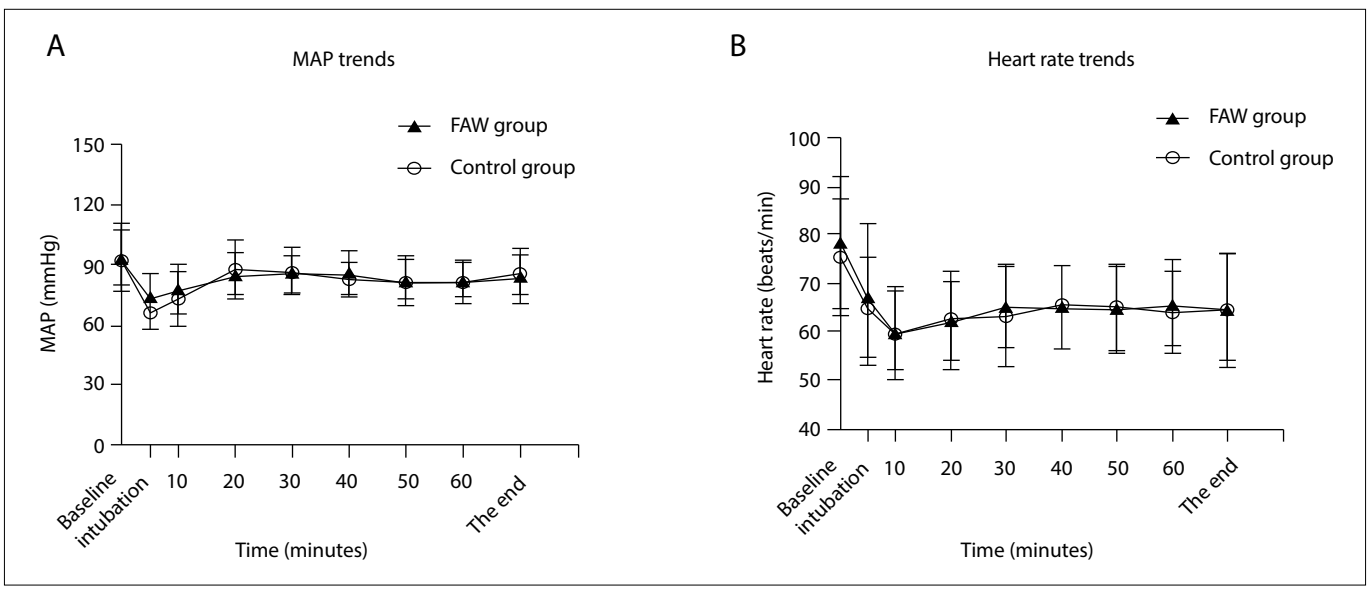

Figure 2. Perioperative hemodynamics. a. Mean arterial pressure (MAP) trends in the two groups. b. Heart rate trends in the two groups. Values are expressed as means ± standard deviation (SD). X axis encompasses the baseline intubation and 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes and 60 minutes after induction of anesthesia. There were no significant differences between the two groups.

heat transfer throughout the surgical procedure and minimized the core temperature loss, which was caused mostly by surgical and anesthesia factors.

It is hard to maintain normothermia at a typical operating room temperature. Some studies have reported that general anesthesia has the capacity to reduce metabolic heat production by about 30%. However, perioperative warming devices may compensate for this.[22]

In our study, hypothermia possibly caused occurrences of PONV, notably at 24 hours after the operation (the rate of occurrence of nausea and vomiting was 6.7% in the FAW group versus 30% in the control group). VAS scores at 24 hours in the FAW group were much lower than those in the control group. This suggested that the patients in the FAW group were in a better physical condition at 24 hours after the operation, with low occurrence of PONV. However, the use of antiemetic drugs in the ward in the two groups was 46.7% in the FAW group and 56.7% in the control group.

Some studies have shown that occurrences of nausea are more resistant to interventions.[23] The data from the ward suggested to us that clinicians in the ward were possibly prescribing antiemetic drugs as prophylaxis for PONV. Quigley et al. stated that most clinically encountered episodes of PONV were typically short-lived and self-limited.[24] Because of the prophylactic antiemetic drugs, the number of times that patients in the FAW group asked for relief from nausea diminished.

In addition, we observed that frequency of occurrence of postoperative shivering increased in the control group. Along with PONV, shivering caused discomfort for the patients recovering from general anesthesia, even though none of them presented temperatures under 35 °C. This possibly implied that pre-warming decreased the risk of surgical complications. Patients were able to absorb nutrients earlier, which was conducive to recovery.[25]

Furthermore, the QoR-40 scores suggested that the higher these were, the faster and better the quality of recovery were. The FAW group showed better status for physical independence (PI) and pain (P) than the control group at 24 hours after the operation. Meanwhile, presence of pain itself increased the occurrences of PONV. Moreover, postoperative opioid administration likewise has been found to give rise to a high risk of PONV.[26] At 48 hours after the operation, the ES scores in the FAW group were clearly higher than those in the control group.

Most patients in both groups lay in a semi-reclining position on the bed. Better body condition and peaceful psychological status would be expected to accelerate rehabilitation. However, we found that for some patients whose psychological status was poor at the outset, their condition could not be improved through surgery because their pessimism affected the functioning of their immune system.[27-29]

Some studies have demonstrated that the medial prefrontal cortex and the pregenual anterior cingulate cortex are involved in people's cognitive and emotion functioning. Vitaly Napadow showed that the presence of stress, emotion and fear conditioning was associated with increasing sensation of nausea in the brain through functional magnetic resonance imaging (fMRI).[30] Some research has suggested that knowledge of the risk factors for nausea and vomiting, along with knowledge of health and affective factors, would lead to healthier behavior.[31,32]

At 24 hours and 48 hours after the operation, the total QoR-40 scores in the FAW group were significantly higher than those in the control group. The quality of recovery in the FAW group suggested that patients with pre-warming were not undergoing any intensely physiological stress reactions, such as PONV, shivering and heat loss.

There were some limitations to this study. Firstly, we did not test any serum biochemical parameters to reflect the patients' inner reactions to nausea and vomiting through maintenance of normal temperature. Secondly, we did not test the PONV intensity scale, which could have provided supplementary data to explain the relationship between prophylactic rewarming and PONV.

CONCLUSIONS

Prophylactic rewarming effectively relieved the condition of PONV and provided some help in improving the quality of postoperative recovery among these patients undergoing laparoscopic hysterectomy.

Table 4. Demographic data of the patients included

Items	FAW group n = 30	Control group n = 30	P
Age; years	48.63 ± 4.41	47.17 ± 4.54	0.21
Body mass index; kg/m^2	22.74 ± 2.66	23.64 ± 2.41	0.173
Duration of operation; minutes	77.30 ± 29.23	91.53 ± 31.91	0.077
Duration of anesthesia; minutes	116.87 ± 132.41	108.63 ± 31.197	0.741
Crystalloids; ml	1033.33 ± 224.89	1000.00 ± 227.43	0.57
Sufentanil; µg	34.80 ± 5.85	35.53 ± 6.54	0.65
Remifentanil; µg	679.00 ± 256.72	728.27 ± 270.34	0.472
Time of extubation, minutes	5.00 ± 3.09	5.83 ± 5.07	0.445

FAW group, forced air warming group; values are expressed as mean ± standard deviation (SD) or number of patients. No significant differences between the two groups.

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Address for correspondence:
DongDong Liang
Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Ouhai Area, Wenzhou city, Zhejiang province, China. 325000
Tel. +86-577-55579372, +86-13758468959
E-mail: amysparks@aliyun.com

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Reverse-transcriptase polymerase chain reaction versus chest computed tomography for detecting early symptoms of COVID-19. A diagnostic accuracy systematic review and meta-analysis

Márcio Luís Duarte[I], Lucas Ribeiro dos Santos[II], Andrea Carla de Souza Contenças[III], Wagner Iared[IV], Maria Stella Peccin[V], Álvaro Nagib Atallah[VI]

Evidence-Based Health Department, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD, MSc. Musculoskeletal Radiologist, WEBIMAGEM, São Paulo (SP), Brazil; Doctoral Student in Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0002-7874-9332

[II]MD, MSc. Endocrinologist and Professor of Physiology and Internal Medicine, Centro Universitário Lusíada (UNILUS), Santos (SP), Brazil; Doctoral Student in Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0001-7897-1198

[III]MD. Pulmonologist and Professor of Emergency Medicine. Centro Universitário Lusíada (UNILUS), Santos (SP), Brazil; Master's Degree Student in Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0003-0070-6401

[IV]MD, PhD. Supervising Professor of the Postgraduate Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0002-6426-5636

[V]PT, PhD. Associate Professor, Department of Human Movement Sciences, and Advisor, Postgraduate Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0003-0329-4588

[VI]MD, PhD. Head of Evidence-Based Health Department, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0003-0890-594X

KEY WORDS (MeSH terms):
COVID-19 [supplementary concept].
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Real-time polymerase chain reaction.
Polymerase chain reaction.
Tomography.
Radiology.

AUTHORS' KEY WORDS:
Ground-glass opacities.
CT scan.
Accuracy.

ABSTRACT

BACKGROUND: A positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS CoV-2, from nasopharyngeal swabs, is the current gold standard diagnostic test for this virus and has sensitivity of 60-70%. Some studies have demonstrated a significant number of false-negative RT-PCR tests while displaying significant tomographic findings, in the early days of symptoms of COVID-19.

OBJECTIVE: To compare accuracy between RT-PCR and computed tomography (CT) for detecting COVID-19 in the first week of its symptoms during the pandemic.

DESIGN AND SETTING: Systematic review of comparative studies of diagnostic accuracy within the Evidence-based Health Program of a federal university in São Paulo (SP), Brazil.

METHODS: A systematic search of the relevant literature was conducted in the PubMed, EMBASE, Cochrane Library, CINAHL and LILACS databases, for articles published up to June 6, 2020, relating to studies evaluating the diagnostic accuracy of RT-PCR and chest CT for COVID-19 diagnoses. The QUADAS 2 tool was used for methodological quality evaluation.

RESULTS: In total, 1204 patients with COVID-19 were evaluated; 1045 had tomographic findings while 755 showed positive RT-PCR for COVID-19. RT-PCR demonstrated 81.4% sensitivity, 100% specificity and 92.3% accuracy. Chest CT demonstrated 95.3% sensitivity, 43.8% specificity and 63.3% accuracy.

CONCLUSION: The high sensitivity and detection rates shown by CT demonstrate that this technique has a high degree of importance in the early stages of the disease. During an outbreak, the higher prevalence of the condition increases the positive predictive value of CT.

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INTRODUCTION

Since COVID-19 pneumonia emerged in Wuhan, China, there has been a search for knowledge that might prevent or minimize its spread.[1–3] In just over three months after its initial breakout, it gained worldwide reach such that it affected more than 2.5 million people, with more than 180,000 deaths in more than 200 countries. COVID-19 is caused by the SARS-CoV-2 virus, a member of the Coronaviridae family.[3] Its transmission occurs mainly through respiratory droplets.[1]

The clinical spectrum of the disease is variable, and the majority of cases are asymptomatic or oligosymptomatic. The most severe cases, with acute respiratory distress syndrome, commonly affect elderly patients with comorbidities.[3]

A positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2, from nasopharyngeal swabs, is the current gold standard diagnostic test. The sensitivity of RT-PCR for SARS-CoV-2 is 50-70%;[4–10] around 30-40% of patients with early-stage COVID-19 are false-negative.[4] An inadequate technique for collecting sampling material or low viral load, limited development of nucleic acid detection technology and variation in the detection rate between different manufacturers may all be determinants for false negative results.[4,11]

Use of computed tomography (CT) is based on the clinical context and time taken to make the diagnosis, especially in relation to use of RT-PCR and other clinical and laboratory investigations.[4,12,13]

CT findings do not alter the diagnosis of COVID-19 in cases in which RT-PCR is positive, but they are useful for grading pulmonary involvement and its evolution.[4,6,8] CT has 56-98% sensitivity,[7] and according to Ai et al., 25% specificity and 68% accuracy.[14]

Ai et al. found that out of 64 patients with an initially negative RT-PCR test, 15 (23.4%) subsequently had a positive RT-PCR (mean time interval of 5.1 ± 1.5 days); ten of these patients (15.6% of those with initial negative RT-PCR) had typical CT findings at the time of the initial negative RT-PCR.[14] Fang et al. described a 29.4% rate of abnormal CT in patients with initially negative and subsequently positive RT-PCR.[4,11]

In the minority of patients with high clinical suspicion in the context of the current pandemic, but with negative initial RT-PCR, the presence of typical CT findings could indicate the possibility of COVID-19 earlier, i.e. before sufficient RT-PCR runs have been done to rule out or confirm the diagnosis.[4,10]

OBJECTIVES

To determine the accuracy of RT-PCR and CT over the first seven days of symptoms of COVID-19 and which method is more sensitive for early case detection.

METHODS

Study model

The study model followed the guidelines for systematic reviews on diagnostic accuracy studies, i.e. Cochrane Diagnostic Reviewer's Handbook version 5.1.

Inclusion criteria

The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We included comparative studies on diagnostic accuracy among patients who underwent both CT and RT-PCR for making the diagnosis of COVID-19 in the initial days of its evolution, regardless of the severity of the disease. We did not put any restrictions on patient age, origin, language or publication status of the study. There was no exclusion regarding population size or patient age. In the case of missing information, the authors of the study in question were contacted by e-mail.

Participants

The participants were men and women of all ages with suspected COVID-19 who underwent chest CT and RT-PCR during their first week of symptoms.

Selection of studies and data extraction

The studies selected were those potentially eligible for inclusion in terms of relevance of the articles or abstracts in indexed journals. Two authors performed independent selections for eligibility. In cases of disagreement, a third author was consulted. Data extraction was performed using a standardized form. The selection process was carried out using the Rayyan platform (https://rayyan.qcri.org).[15]

Evaluation of methodological quality

The QUADAS 2 tool, which is used to evaluate bias and precision, was used in relation to all the eligible studies.[16] All analyses and diagrams were completed using RevMan 5.3 and MetaDisc 1.4. The study was approved by our institutional review board, under approval number: 8483190420; date: May 4, 2020. The review was registered in the Open Science Framework database.

Research methods for selecting studies

A thorough systematic search of the relevant literature was conducted in the PubMed, EMBASE, Cochrane Library, CINAHL and LILACS online scientific publication databases, for original articles published up to June 6, 2020, with no language restrictions. The search used the following Medical Subject Headings (MeSH terms): COVID-19; SARS virus; coronavirus infection; Real-Time Polymerase Chain Reaction; Polymerase Chain Reaction; and Tomography, X-Ray Computed. The reference lists of the studies included and the main reviews on the subject were also evaluated. Manual searches were also carried out in these reference lists. The full search strategy is displayed in **Table 1**.

RESULTS

Studies selected

The systematic review yielded 168 studies. At the end of the analysis, five studies. [9,11,14,17,18] were deemed to meet the inclusion criteria and presented acceptable quality according to the QUADAS 2 tool. These studies were thus included in the systematic review (**Figure 1**). Among these, two studies were included in the meta-analysis.[9,17]

In all the studies, there was high concern about applicability. Moreover, in three of the five studies, a high risk of bias was also perceived. It was not clear in most studies whether the radiologist who reported the CT scan had access to the RT-PCR results (**Figure 2**).

Analysis on the studies

Table 2 provides a summary of the findings from the main studies included. In total, 1204 patients with COVID-19 that were evaluated. Among these, 1045 had tomographic findings (detection rate of 86.7%) and 755 showed positive RT-PCR for COVID-19 (detection rate of 62.7%), with a significant difference in detection rate of 24.0%.

Table 1. Search strategy according to the corresponding database

Database	Search strategy
Cochrane Library	#1 MeSH descriptor: [SARS Virus] explode all trees #2 MeSH descriptor: [Coronavirus Infections] explode all trees #3 MeSH descriptor: [Real-Time Polymerase Chain Reaction] explode all trees #4 MeSH descriptor: [Polymerase Chain Reaction] explode all trees #5 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees #6: #1 OR #2 AND #3 OR #4 AND #5
MEDLINE	#1: "COVID-19 [Supplementary Concept]"[MeSH] OR (2019 novel coronavirus infection) OR (COVID19) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (2019-nCoV disease) OR (2019 novel coronavirus disease) OR (2019-nCoV infection) OR "SARS Virus"[MeSH] OR (Severe Acute Respiratory Syndrome Virus) OR (SARS-Related Coronavirus) OR (Coronavirus, SARS-Related) OR (SARS Related Coronavirus) OR (SARS-CoV) OR (Urbani SARS-Associated Coronavirus) OR (Coronavirus, Urbani SARS-Associated) OR (SARS-Associated Coronavirus, Urbani) OR (Urbani SARS Associated Coronavirus) OR (SARS Coronavirus) OR (Coronavirus, SARS) OR (Severe acute respiratory syndrome-related coronavirus) OR (Severe acute respiratory syndrome related coronavirus) OR (SARS-Associated Coronavirus) OR (Coronavirus, SARS-Associated) OR (SARS Associated Coronavirus) OR "Coronavirus Infections"[MeSH] OR (Coronavirus Infection) OR (Infection, Coronavirus) OR (Infections, Coronavirus) OR (Middle East Respiratory Syndrome) OR (MERS (Middle East Respiratory Syndrome)) #2: "Real-Time Polymerase Chain Reaction"[MeSH] OR (Real Time Polymerase Chain Reaction) OR (Real-Time PCR) OR (PCR, Real-Time) OR (PCRs, Real-Time) OR (Real Time PCR) OR (Real-Time PCRs) OR (Kinetic Polymerase Chain Reaction) OR (Quantitative Real-Time Polymerase Chain Reaction) OR (Quantitative Real Time Polymerase Chain Reaction) OR (Quantitative Real-Time PCR) OR (PCR, Quantitative Real-Time) OR (PCRs, Quantitative Real-Time) OR (Quantitative Real Time PCR) OR (Quantitative Real-Time PCRs) OR (Real-Time PCR, Quantitative) OR (Real-Time PCRs, Quantitative) OR "Polymerase Chain Reaction"[MeSH] OR (Polymerase Chain Reactions) OR (Reaction, Polymerase Chain) OR (Reactions, Polymerase Chain) OR (PCR) OR (Inverse PCR) OR (PCR, Inverse) OR (Inverse Polymerase Chain Reaction) OR (Nested Polymerase Chain Reaction) OR (Nested PCR) OR (PCR, Nested) OR (Anchored PCR) OR (PCR, Anchored) OR (Anchored Polymerase Chain Reaction) #3: "Tomography, X-Ray Computed"[MeSH] OR (X-Ray Computed Tomography) OR (Tomography, X-Ray Computerized) OR (Tomography, X Ray Computerized) OR (Computed X Ray Tomography) OR (X-Ray Computer Assisted Tomography) OR (X Ray Computer Assisted Tomography) OR (Tomography, X-Ray Computer Assisted) OR (Tomography, X Ray Computer Assisted) OR (Computerized Tomography, X Ray) OR (Computerized Tomography, X-Ray) OR (X-Ray Computerized Tomography) OR (CT X Ray) OR (CT X Rays) OR (X Ray, CT) OR (X Rays, CT) OR (Tomodensitometry) OR (Tomography, X Ray Computed) OR (X Ray Tomography, Computed) OR (X-Ray Tomography, Computed) OR (Computed X-Ray Tomography) OR (Tomographies, Computed X-Ray) OR (Tomography, Computed X-Ray) OR (Tomography, Xray Computed) OR (Computed Tomography, Xray) OR (Xray Computed Tomography) OR (CAT Scan, X Ray) OR (CAT Scan, X-Ray) OR (CAT Scans, X-Ray) OR (Scan, X-Ray CAT) OR (Scans, X-Ray CAT) OR (X-Ray CAT Scan) OR (X-Ray CAT Scans) OR (Tomography, Transmission Computed) OR (Computed Tomography, Transmission) OR (Transmission Computed Tomography) OR (CT Scan, X-Ray) OR (CT Scan, X Ray) OR (CT Scans, X-Ray) OR (Scan, X-Ray CT) OR (Scans, X-Ray CT) OR (X-Ray CT Scan) OR (X-Ray CT Scans) OR (Computed Tomography, X-Ray) OR (Computed Tomography, X Ray) OR (X Ray Computerized Tomography) OR (Cine-CT) OR (Cine CT) OR (Electron Beam Computed Tomography) OR (Electron Beam Tomography) OR (Beam Tomography, Electron) OR (Tomography, Electron Beam) OR (Tomography, X-Ray Computerized Axial) OR (Tomography, X Ray Computerized Axial) OR (X-Ray Computerized Axial Tomography) OR (X Ray Computerized Axial Tomography) #4: #1 AND #2 AND #3
EMBASE (OvidSP)	#1: 'covid 19'/exp OR 'SARS coronavirus'/exp OR 'Coronavirus infection'/exp #2: 'pcr assay kit'/exp OR 'real time polymerase chain reaction'/exp OR 'polymerase chain reaction'/exp #3: 'x-ray computed tomography'/exp #4: #1 AND #2 AND #3

Continue...

Table 1. Continuation.

Database	Search strategy
	#1: MH:"SARS Virus" OR (Virus del SRAS) OR (Vírus da SARS) OR (CoV-SARS) OR (CoV-SRAG) OR (Coronavirus Associado a SARS) OR (Coronavirus Relacionado à Síndrome Respiratória Aguda Grave) OR (SARS-CoV) OR (SRAG-CoV) OR (Vírus SARS) OR (Vírus da Pneumonia Asiática) OR (Vírus da Síndrome Respiratória Aguda Grave) OR (Vírus da Síndrome Respiratória Aguda Severa) OR MH:B04.820.504.540.150.113.937$ OR (covid-19) OR (2019 novel coronavirus infection) OR (COVID19) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (2019-nCoV disease) OR (2019 novel coronavirus disease) OR (2019-nCoV infection) #2: MH:"Real-Time Polymerase Chain Reaction" OR (Reacción en Cadena en Tiempo Real de la Polimerasa) OR (Reação em Cadeia da Polimerase em Tempo Real) OR (Kinetic Polymerase Chain Reaction) OR (PCR, Quantitative Real-Time) OR (PCR, Real-Time) OR (PCRs, Quantitative Real-Time) OR (PCRs, Real-Time) or (Quantitative Real Time PCR) OR (Quantitative Real Time Polymerase Chain Reaction) OR (Quantitative Real-Time PCR) OR (Quantitative Real-Time PCRs) OR (Quantitative Real-Time Polymerase Chain Reaction) OR (Real Time PCR) OR (Real Time Polymerase Chain Reaction) OR (Real-Time PCR) OR (Real-Time PCR, Quantitative) OR (Real-Time PCRs) OR (Real-Time PCRs, Quantitative) OR MH:E05.393.620.500.706$ OR MH:"Polymerase Chain Reaction" OR (Reacción en Cadena de la Polimerasa) OR (Reação em Cadeia da Polimerase) OR (Anchored Polymerase Chain Reaction) OR (Inverse PCR) or (Inverse Polymerase Chain Reaction) OR (Nested PCR) or (Nested Polymerase Chain Reaction) OR (PCR) or (PCR, Anchored) OR (PCR, Inverse) OR (PCR, Nested) OR (Polymerase Chain Reactions) OR (Reaction, Polymerase Chain) OR (Reactions, Polymerase Chain) OR MH:E05.393.620.500$
LILACS	#3: MH:"Tomography, X-Ray Computed" OR (Tomografía Computarizada por Rayos X) OR (Tomografia Computadorizada por Raios X) OR (Beam Tomography, Electron) or (CAT Scan, X Ray) OR (CAT Scan, X-Ray) OR (CAT Scans, X-Ray) OR (CT Scan, X Ray) OR (CT Scan, X-Ray) OR (CT Scans, X-Ray) OR (CT X Ray) OR (CT X Rays) OR (Cine CT) OR (Cine-CT) OR (Computed Tomography, Transmission) OR (Computed Tomography, X Ray) OR (Computed Tomography, X-Ray) OR (Computed Tomography, Xray) OR (Computed X Ray Tomography) OR (Computed X-Ray Tomography) OR (Computerized Tomography, X Ray) OR (Computerized Tomography, X-Ray) OR (Electron Beam Computed Tomography) OR (Electron Beam Tomography) OR (Scan, X-Ray CAT) OR (Scan, X-Ray CT) OR (Scans, X-Ray CAT) OR (Scans, X-Ray CT) OR (Tomodensitometry) OR (Tomographies, Computed X-Ray) OR (Tomography, Computed X-Ray) OR (Tomography, Electron Beam) OR (Tomography, Transmission Computed) OR (Tomography, X Ray Computed) OR (Tomography, X Ray Computer Assisted) OR (Tomography, X Ray Computerized) OR (Tomography, X Ray Computerized Axial) OR (Tomography, X-Ray Computer Assisted) OR (Tomography, X-Ray Computerized) OR (Tomography, X-Ray Computerized Axial) OR (Tomography, Xray Computed) OR (Transmission Computed Tomography) OR (X Ray Computer Assisted Tomography) OR (X Ray Computerized Axial Tomography) OR (X Ray Computerized Tomography) OR (X Ray Tomography, Computed) OR (X Ray, CT) OR (X Rays, CT) OR (X-Ray CAT Scan) OR (X-Ray CAT Scans) OR (X-Ray CT Scan) OR (X-Ray CT Scans) OR (X-Ray Computed Tomography) OR (X-Ray Computer Assisted Tomography) OR (X-Ray Computerized Axial Tomography) OR (X-Ray Computerized Tomography) OR (X-Ray Tomography, Computed) OR (Xray Computed Tomography) or (mh:E01.370.350.350.810$) OR MH:E01.370.350.600.350.700.810$) OR MH:E01.370.350.700.700.810$ OR MH:E01.370.350.700.810.810$ OR MH:E01.370.350.825.810.810$ #4: #1 AND #2 AND #3
	#1: (SARS Virus) or (CoV-SARS) or (CoV-SRAG) or (Coronavirus Associado a SARS) or (Coronavirus Relacionado à Síndrome Respiratória Aguda Grave) or (SARS-CoV) or (SRAG-CoV) or (Vírus SARS) or (Vírus da Pneumonia Asiática) or (Vírus da Síndrome Respiratória Aguda Grave) or (Vírus da Síndrome Respiratória Aguda Severa) OR (COVID-19) OR (2019 novel coronavirus infection) OR (COVID19) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (2019-nCoV disease) OR (2019 novel coronavirus disease) OR (2019-nCoV infection) #2: (Real-Time Polymerase Chain Reaction) OR (Real Time Polymerase Chain Reaction) OR (Real-Time PCR) OR (PCR, Real-Time) OR (PCRs, Real-Time) OR (Real Time PCR) OR (Real-Time PCRs) OR (Kinetic Polymerase Chain Reaction) OR (Quantitative Real-Time Polymerase Chain Reaction) OR (Quantitative Real Time Polymerase Chain Reaction) OR (Quantitative Real-Time PCR) OR (PCR, Quantitative Real-Time) OR (PCRs, Quantitative Real-Time) OR (Quantitative Real Time PCR) OR (Quantitative Real-Time PCRs) OR (Real-Time PCR, Quantitative) OR (Real-Time PCRs, Quantitative) OR (Polymerase Chain Reaction) OR (Polymerase Chain Reactions) OR (Reaction, Polymerase Chain) OR (Reactions, Polymerase Chain) OR (PCR) OR (Inverse PCR) OR (PCR, Inverse) OR (Inverse Polymerase Chain Reaction) OR (Nested Polymerase Chain Reaction) OR (Nested PCR) OR (PCR, Nested) OR (Anchored PCR) OR (PCR, Anchored) OR (Anchored Polymerase Chain Reaction)
CINAHL	#3: (Tomography, X-Ray Computed) OR (X-Ray Computed Tomography) OR (Tomography, X-Ray Computerized) OR (Tomography, X Ray Computerized) OR (Computed X Ray Tomography) OR (X-Ray Computer Assisted Tomography) OR (X Ray Computer Assisted Tomography) OR (Tomography, X-Ray Computer Assisted) OR (Tomography, X Ray Computer Assisted) OR (Computerized Tomography, X Ray) OR (Computerized Tomography, X-Ray) OR (X-Ray Computerized Tomography) OR (CT X Ray) OR (CT X Rays) OR (X Ray, CT) OR (X Rays, CT) OR (Tomodensitometry) OR (Tomography, X Ray Computed) OR (X Ray Tomography, Computed) OR (X-Ray Tomography, Computed) OR (Computed X-Ray Tomography) OR (Tomographies, Computed X-Ray) OR (Tomography, Computed X-Ray) OR (Tomography, Xray Computed) OR (Computed Tomography, Xray) OR (Xray Computed Tomography) OR (CAT Scan, X Ray) OR (CAT Scan, X-Ray) OR (CAT Scans, X-Ray) OR (Scan, X-Ray CAT) OR (Scans, X-Ray CAT) OR (X-Ray CAT Scan) OR (X-Ray CAT Scans) OR (Tomography, Transmission Computed) OR (Computed Tomography, Transmission) OR (Transmission Computed Tomography) OR (CT Scan, X-Ray) OR (CT Scan, X Ray) OR (CT Scans, X-Ray) OR (Scan, X-Ray CT) OR (Scans, X-Ray CT) OR (X-Ray CT Scan) OR (X-Ray CT Scans) OR (Computed Tomography, X-Ray) OR (Computed Tomography, X Ray) OR (X Ray Computerized Tomography) OR (Cine-CT) OR (Cine CT) OR (Electron Beam Computed Tomography) OR (Electron Beam Tomography) OR (Beam Tomography, Electron) OR (Tomography, Electron Beam) OR (Tomography, X-Ray Computerized Axial) Ography, X Ray Computerized Axial) OR (X-Ray Computerized Axial Tomography) OR (X Ray Computerized Axial Tomography) #4: #1 AND #2 AND #3

Regarding tomographic pattern changes, Ai et al.[14] found that out of their 888 patients with positive CT results, 409 showed ground-glass opacities and 447 had consolidations; 801 had bilateral findings. Also, 42% of the patients showed improvement on CT before the RT-PCR became negative; and 3.5% showed worsened CT with negative RT-PCR. The CT sensitivity was 96.5% and its specificity was 25.4%; the positive predictive value was 65.3% and the negative predictive value was 83.3%. The first RT-PCR performed on the patients presented sensitivity of 59.2%.

Bernheim et al. evaluated patients divided into three groups concerning the onset of symptoms: early (0-2 days), intermediate (3-5 days) and late (6-12 days). They found that 56% (20 patients out of 36) had an absence of ground-glass opacity and consolidation in the first two days, while 9.0% (three patients out of 33) showed this in the intermediate group and 4% (one patient out of 25) in the late group. RT-PCR was positive in 91.6% of the patients in the early group (33 patients out of 36); 84.4% in the intermediate group (28 patients out of 33); and 92.0% in the late group (23 patients out of 25). One patient with absence of ground-glass opacity and consolidation in the early group showed negative RT-PCR findings. RT-PCR presented sensitivity of 88.4% and CT of 66.6% over the first five days of symptoms.

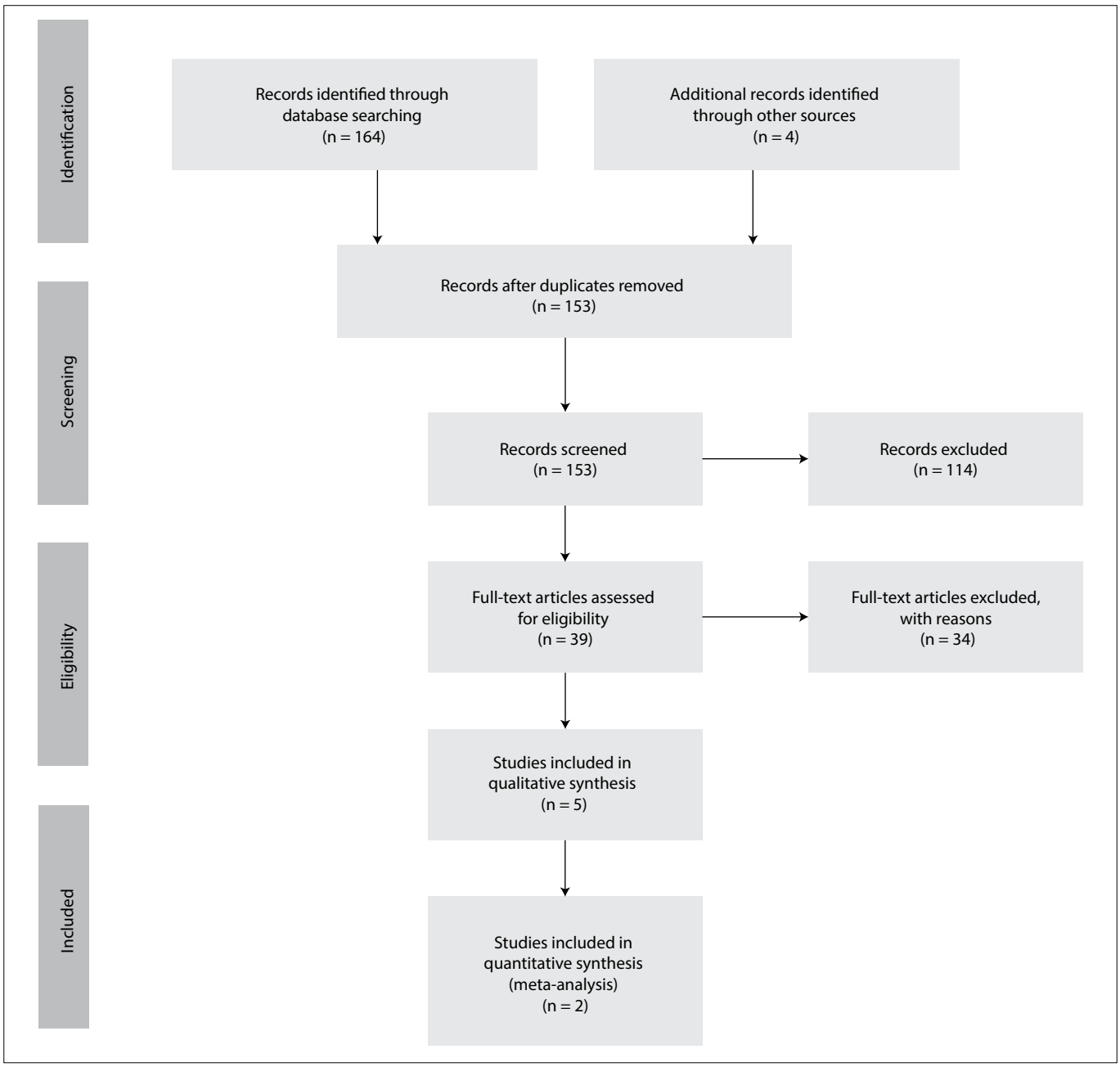

Figure 1. PRISMA 2009 flow diagram.

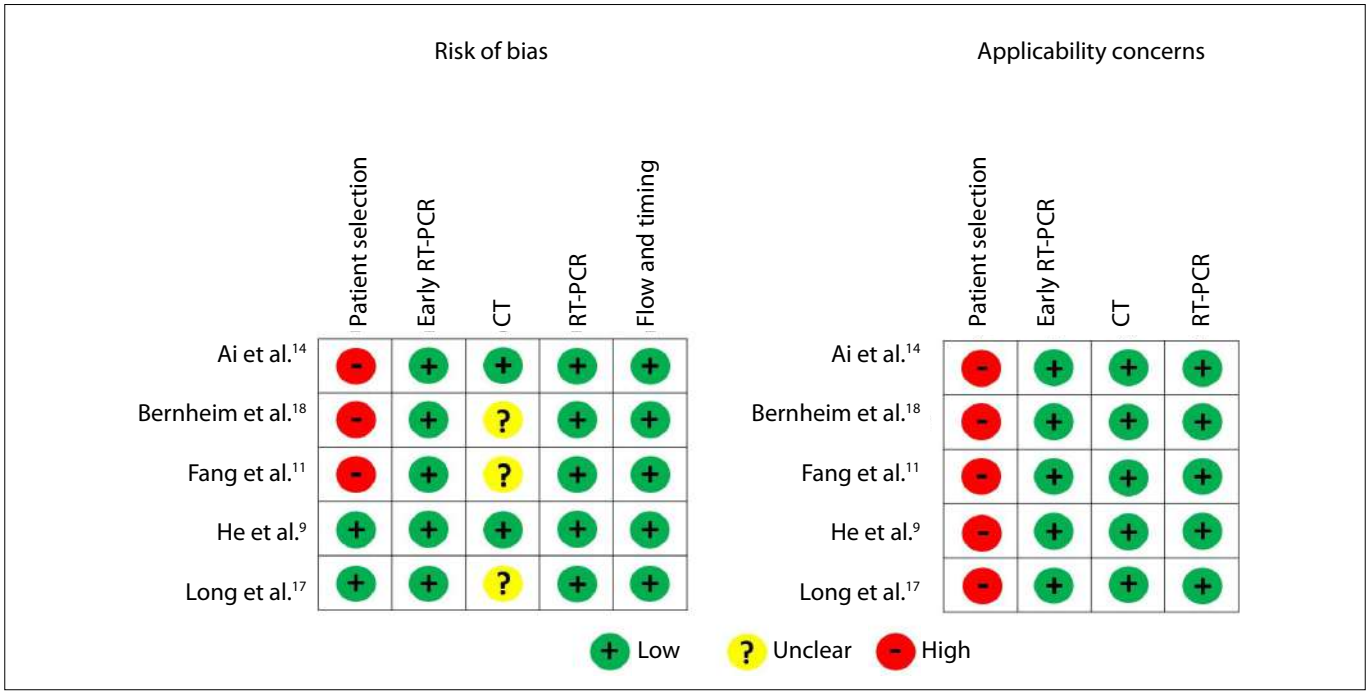

Figure 2. QUADAS 2 risk of bias and applicability concerns.

Table 2. Summary of study findings

Study	Total number of COVID-19 patients included	Positive early RT-PCR	Positive early CT	Comments
Ai 2020[14]	1014	601	888	Average interval between tests: 1 day (less than or equal to 7 days). 308 patients had negative RT-PCR and positive CT. 21 patients had positive RT-PCR and negative CT. 580 patients with positive RT-PCR had positive CT. 258 multiple RT-PCR: average conversion time was 5 days. 10 out of 15 RT-PCR conversions had CT findings when the RT-PCR was negative.
Bernheim 2020[18]	121	61 out of 69 tested in the early and intermediate group	46 out of 69 tested in the early and intermediate group	121 patients divided in three groups: Early group: 0-2 days of symptoms. Intermediate group: 3-5 days of symptoms. Late group: 6-12 days of symptoms.
Fang 2020[11]	51	36	50	Average time between symptoms and CT or RT-PCR: 3 days
He 2020[9]	34	27	26	Performed both tests in the first 2-5 days of symptoms. 48 initial RT-PCR were true negative. 7 initial RT-PCR were false negative. 46 CT were true negative. 8 CT were false positive. 2 CT were false negative.
Long 2020[17]	36	30	35	Performed both tests during the initial presentation of the disease. 30 patients had positive RT-PCR and 35 had positive CT. 6 patients had negative RT-PCR and positive CT. 1 patient had negative CT and positive RT-PCR. 51 patients had negative RT-PCR and positive CT.

In the study by Fang et al.,[11] study, 36 CT-positive cases showed typical changes: sparse, subpleural and peripheral ground-glass opacities, commonly in the lower lobes. The CT sensitivity was 98.0%. The first RT-PCR performed on the patients presented sensitivity of 70.5%.

He et al.[9] compared use of CT and RT-PCR among 82 patients with suspected pneumonia, including COVID-19 pneumonia. The two experienced radiologists who evaluated all chest CT scans demonstrated good interobserver agreement. All the patients underwent chest CT and initial RT-PCR on the same day. The 34 COVID-19 patients had confirmation through RT-PCR, but not necessarily from the initial RT-PCR. The initial RT-PCR had 79% sensitivity, 100% specificity and 92% accuracy. The chest CT had 77% sensitivity, 96% specificity and 88% accuracy. He et al. also analyzed the two tests used in conjunction, and concluded that jointly they presented 88% sensitivity, 100% specificity and 98% accuracy.[9] In the study by He et al.,[9] eight patients with tomographic changes had pneumonia other than COVID-19. It was possible to calculate the positive predictive value of CT, which was 85.1%.

Long et al.[17] also compared the tomographic findings of patients with COVID-19 pneumonia and non-COVID-19 pneumonia. The upper lobes of the lungs were more affected on CT in COVID-19 cases (right: 52.7% versus 37.3%; left: 55.6% versus 33.3%); the other lobes did not show any significant difference. There was also a difference in peripheral involvement, which was more common in cases of pneumonia caused by COVID-19. The sensitivity of CT was 97.2%. The first RT-PCR performed on the patients presented sensitivity of 84.6% and the negative predictive value was 89.4%. In the study by Long et al.,[17] 51 patients with tomographic findings had pneumonia other than COVID-19. This makes it possible to infer that CT presents high specificity. The positive predictive value for CT was calculated as 58.6%.

Accuracy assessment

In the accuracy evaluations of the studies by He and Long,[9,17] RT-PCR demonstrated 81.4% sensitivity (95% confidential interval: 70.3-89.7%) and 100% specificity (95% confidential interval: 96.3-100%), with P-value lower than 0.05, and 92.3% accuracy (**Figures 3 and 4**). In the same studies, CT demonstrated 95.3% sensitivity (95% confidential interval: 86.9-99.0%) and 43.8% specificity (95% confidential interval: 34.1-53.8%), with P-value lower than 0.05, and 63.3% accuracy (**Figures 5 and 6**).

All the data in these five studies were retrospective and were obtained during the epidemic period in the regions where these studies were conducted.

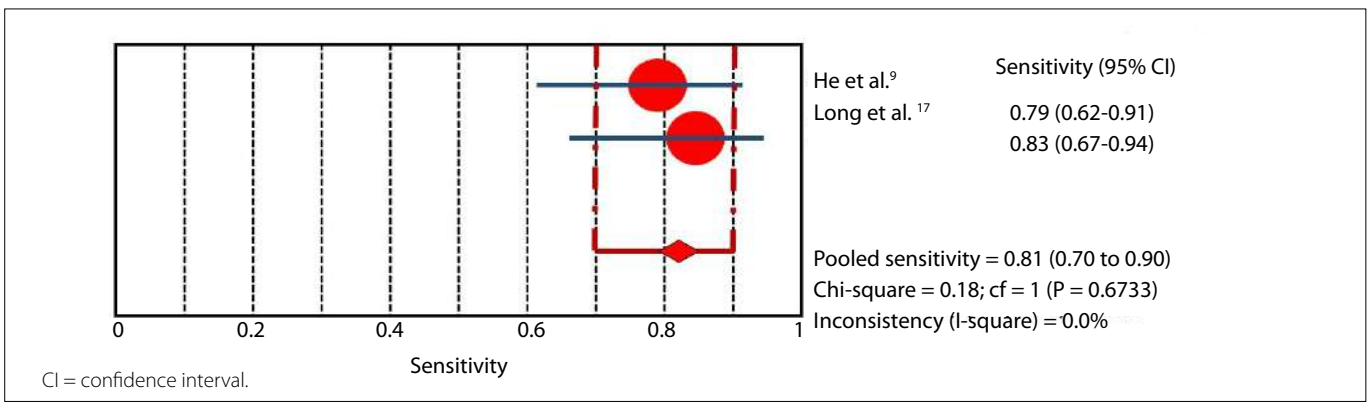

Figure 3. Sensitivity graph: RT-PCR.

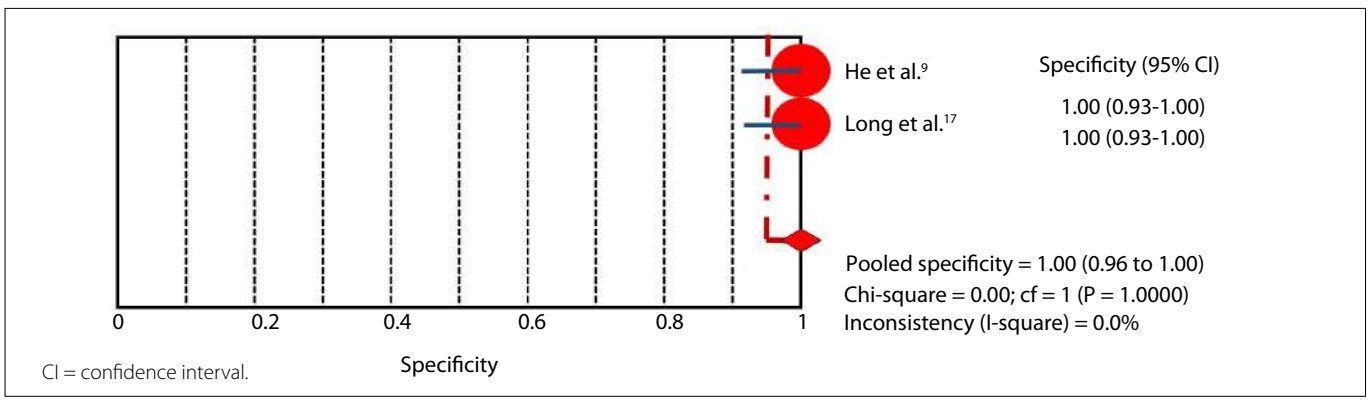

Figure 4. Specificity graph: RT-PCR.

DISCUSSION

The symptoms of COVID-19 consist mainly of fever, fatigue and dry cough, with gradual dyspnea in some cases, and acute respiratory distress syndrome and multiple organ dysfunction in severe cases requiring intensive treatment.[1,2,19,20] While the majority of patients, about 80%, have mild symptoms; older patients, especially those above 70 years old and those with underlying conditions, such as cardiovascular disease, diabetes, chronic respiratory diseases and oncological diseases, have a higher mortality rate of up to 15%.[3]

In addition to the most common pattern of peripheral and bilateral ground-glass injuries, other patterns of lung injury may be observed.[6,7,20-25] Pulmonary consolidations are present in 2-64% of the cases and form an indicator of disease progression, thus serving as a warning sign for the severity of the patient's condition. Reticular pattern lesions have lower incidence than consolidations and opacities.[6,26]

The crazy-paving pattern is present in about 5-36% of the cases, while bronchial wall thickening is present in 10-20%.[6,27] Pleural changes are present in 32%, with pleural thickening; however, pleural effusion occurs in only 5% of the cases.[6,24] Pulmonary fibrosis occurs in 17% of the cases and pulmonary nodules smaller than three centimeters in size, in 3-13%.[6] The incidence of lymph node enlargement is about 4-8% and pericardial effusion occurs in approximately 5%. The latter is an indicator of severity.[6,19] Vascular thickening is characterized in 59% of the cases.[7] The radiological findings tend to become worse seven days after the onset of symptoms and show improvement 14 days after the onset of symptoms.[3]

In the current pandemic situation, despite the low specificity of CT (25%), this technique can be used to isolate patients and institute treatment at an early stage, since it presents sensitivity of about 88.9%, starting from the early day of symptoms.[4,10,20,28] In comparison with this, chest X-ray shows abnormalities in 59.1% of the cases and in 76.7% among serious cases.[4,23]

Xie et al.[29] reported on a case series in which they performed RT-PCR and CT on the same day, regardless of the duration of the patients' symptoms. They found that out of their 167 patients, 162 were positive according to RT-PCR and 160 were positive according to CT. Seven patients were positive on RT-PCR and negative on CT; and five patients were positive on CT and negative on RT-PCR. CT presented 95.0% of sensitivity, while RT-PCR presented 97.0%. Concerning false-negative data, CT showed 4.0%.

Barbosa et al. evaluated 91 patients with suspected pneumonia until 30 days after their initial symptoms and performed RT-PCR and chest CT on the same day. Sixty-three of their patients had symptoms for seven days or less and, among these patients, two were positive on RT-PCR and negative on CT, with a CT false-negative rate of 3.1%. For 28 patients, both tests were negative; and for 15, both tests were positive.[10]

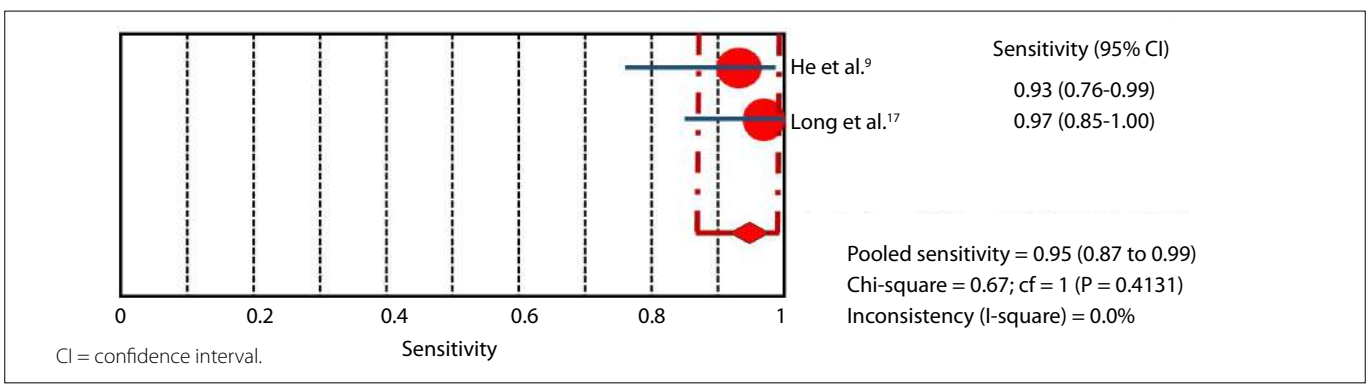

Figure 5. Sensitivity graph: chest CT.

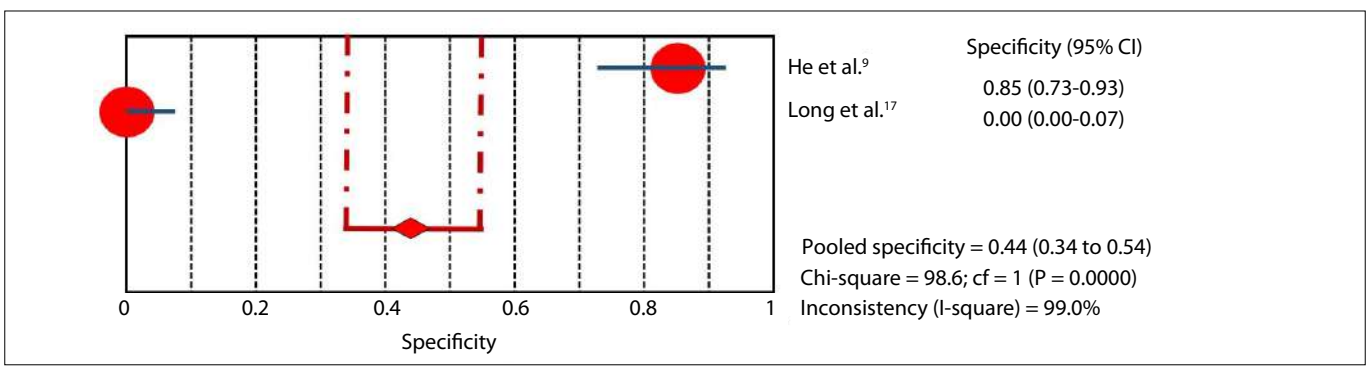

Figure 6. Specificity graph: chest CT.

It should, however, be noted that a normal CT scan cannot be used to rule out a diagnosis of COVID-19,[21,26,30] although there is some evidence to suggest that the negative predictive value of CT is greater for symptoms lasting longer than one week.[4] It also needs to be taken into account that CT may be normal in cases with positive RT-PCR in 2-20% cases, according to studies by Yang et al., Guan et al. and Chung et al.[4,19,23,31]

Moreover, 54-70.8% of asymptomatic people who have had contact with symptomatic patients and who are COVID-19-positive according to RT-PCR may present a change on CT.[4,5,32] Long et al. analyzed 37 asymptomatic individuals, who had come into contact with RT-PCR-confirmed patients, and reported that 21 (56.7%) of these individuals had positive CT findings.[33] Inui et al.[5] detected pulmonary opacity on CT in 24 out of 30 symptomatic patients (80%); however, in 82 asymptomatic patients, 44 (54%) had opacities on CT.[5] Shi et al. also reported occurrences of CT abnormalities in asymptomatic patients.[24] Furthermore, in symptomatic cases, they found greater extent of the lesion, along with areas of consolidation predominating over ground-glass opacities.[5,24]

Bai et al. assessed the performance of radiologists in differentiating CT results between those from patients with COVID-19 pneumonia and those from patients with non-COVID-19 pneumonia.[7] These radiologists achieved accuracy ranging from 72 to 97%, with sensitivity of 70-94% and greatly varying specificity (24-94%).[7]

Therefore, the role of CT in confirmed cases of COVID-19 after the results from RT-PCR have been obtained is the same as in relation to any other viral infection, in that it can be used to do the following:[4]

- Add diagnostic value for patients with pre-existing lung diseases.
- Help diagnose complications or investigate a clinically discordant condition: positive to negative turnover RT-PCR, but increased hypoxia.
- Find coexisting or underlying diagnoses.

Although CT is very sensitive at the onset of symptoms, in comparison with RT-PCR, it still may not reveal the characteristic pattern of COVID-19 in all cases. Hence, it remains difficult to differentiate COVID-19 from other viral causes of pneumonia.[7] According to Bai et al., although making the diagnosis of pneumonia due to COVID-19 is possible via CT, subtle or atypical presentations can lead to a wrong diagnosis.[7]

Our findings showed that CT outperformed RT-PCR in making an early diagnosis of COVID-19 in suspected cases. Both from previous findings and ours, we suggest that an early evaluation protocol should include applying CT when RT-PCR is negative. This could guide clinicians' treatment and patient isolation criteria, in order to avoid virus dissemination. Our meta-analysis showed that CT had specificity of 43.8% and sensitivity of 95.3%, and both of these values are higher than those in the recent literature.

All the studies evaluated were conducted among in patients with COVID-19 that confirmed within the first seven days of symptoms by means of RT-PCR. However, this test was not necessarily the first to be performed on suspected patients, within the epidemic period in the country in which these tests were performed. Therefore, the positive predictive value and detection rate of CT findings in patients with COVID-19 will be higher than it would be outside the epidemic period.

Although RT-PCR is the gold standard for diagnosing COVID-19, it presents a significant percentage of false-negative tests in the early days of symptoms of the disease (0-7 days). On the other hand, even though CT is a test with presumably low specificity,[26] thereby allowing several differential diagnoses,[8] it detects patterns compatible with COVID-19. It has presented very high sensitivity and significant positive predictive value and detection rate in the epidemic period.[8,26]

CONCLUSION

The high sensitivity and detection rate of CT demonstrate that it has a high degree of importance in the early stages of the disease, even greater than RT-PCR. During an outbreak, the higher prevalence of the condition raises the positive predictive value of CT. However, the low specificity of CT (43.8%) also needs to be considered. Outside of pandemic times, its positive predictive value for this condition should decrease proportionally with the decline in the prevalence of the disease in the population.

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(equal), writing-original draft (equal) and writing-review and editing (equal); Contenças ACS: data curation (equal), formal analysis (equal), resources (equal), software (equal) and supervision (equal); Iared W: investigation (equal), methodology (equal), project administration (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Peccin MS: formal analysis (equal), funding acquisition (equal), resources (equal), software (equal) and writing-review and editing (equal); and Atallah AN: methodology (equal), validation (equal), visualization (equal) and writing-review and editing (equal). All authors approved the final version of the manuscript for publication

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Address for correspondence:
Márcio Luís Duarte
R. Napoleão de Barros, 865
Vila Clementino — São Paulo (SP) — Brasil
CEP 04024-002
Tel. (+55 11) 5576-4848
E-mail: marcioluisduarte@gmail.com

Investigation of mental health among hospital workers in the COVID-19 pandemic: a cross-sectional study

Songül Araç[I], Süleyman Dönmezdil[II]

Department of Emergency Medicine, University of Health Sciences, Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Diyarbakır, Turkey

[I]MD. Assistant Professor, Department of Emergency Medicine, University of Health Sciences, Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Diyarbakır, Turkey.
orcid.org/0000-0001-6830-3639

[II]MD. Assistant Professor, Department of Psychiatry, University of Health Sciences, Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Diyarbakır, Turkey.
orcid.org/0000-0002-7171-1374

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ABSTRACT

BACKGROUND: The rapid spread of the COVID-19 epidemic has led to extraordinary measures taken worldwide, and has led to serious psychological disorders. Healthcare professionals face greater severity of stress burden, due both to their direct contact with patients with the virus and to the isolation dimension of this outbreak.

OBJECTIVE: To examine psychiatric disorders such as anxiety, depression and sleep disorders among healthcare professionals working in an emergency department and a COVID-19 clinic.

DESIGN AND SETTING: Cross-sectional study including healthcare professionals in the emergency department and other units serving patients with COVID-19, of a training and research hospital in Turkey.

METHODS: 210 volunteers, including 105 healthcare professionals in the emergency department and 105 healthcare professionals working in other departments rendering services for COVID-19 patients, were included in this study. A sociodemographic data form and the Hospital Anxiety Depression Scale (HAD), Pittsburg Sleep Quality Index (PSQI), World Health Organization Quality of Life scale (WHOQOL-BREF-TR) and Religious Orientation Scale were applied to the volunteers.

RESULTS: The perceived stress levels and PSQI subscores were found to be significantly higher among the volunteers working in the emergency department than among those in other departments. The risk of development of anxiety among women was 16.6 times higher than among men.

CONCLUSIONS: Healthcare professionals on the frontline need systematic regular psychosocial support mechanisms. Anxiety due to fear of infecting family members can be prevented through precautions such as isolation. However, it should be remembered that loneliness and feelings of missing family members consequent to isolation may increase the risk of depression.

INTRODUCTION

A new virus that emerged in Wuhan, China, in 2019 has been found to spread quickly and cause pneumonia, leading to severe respiratory failure. It was named SARS-CoV-2 due to its close resemblance to SARS-CoV, and the disease was named COVID-19. The virus spread rapidly across China and has become a significant health problem worldwide. Considering the rate of spreading of the virus, COVID-19 was declared to be a pandemic by the World Health Organization (WHO) on March 12, 2020. As of April 30, 2020, the number of cases had exceeded 118,000 in Turkey and 3,190,000 worldwide. Although mortality rates vary from country to country and according to the number of tests performed, the mortality rate in Turkey is approximately 2.33%.[1,2]

Upon the announcement declaring COVID-19 to be a pandemic, measures were quickly implemented in Turkey and worldwide. Some of the warnings issued by the authorities related to anxiety and post-traumatic stress disorder that may arise in the community, in connection with exposure to the virus.[3] The rapid spread of the epidemic in countries such as Italy and Spain, and the disruptions to the healthcare systems of these countries, led to rapid organization of the healthcare system in Turkey. COVID-19 hospitals were designated and planning was undertaken with regard to patient admission, diagnosis, treatment protocols and work systems for the healthcare staff employed in these locations.

In addition to these measures, numerous meetings were held and training sessions were organized with the aim of informing healthcare professionals about the virus in Turkey, as was done in many countries with the outbreak. However, because there are many unknowns about the virus and because healthcare professionals have to perform triage for treatments in countries where the outbreak is very severe, the anxiety levels among healthcare professionals have

risen.[4,5] During this challenging process, these high levels of anxiety among healthcare professionals will naturally be neglected and will not receive the necessary attention. Nonetheless, this issue should not be ignored, since neglect now may lead to problems that are difficult to solve later on.

Many psychiatric disorders may occur in situations of disease outbreaks or natural disasters. Among these disorders, anxiety, depression and post-traumatic stress disorder are the most common. A study conducted in China among healthcare workers involved in the COVID-19 outbreak supports this idea. In that study, Kang et al.[4] found that anxiety, depression and sleep disorder scale scores were significantly higher among physicians and nurses.

Unless corrected through adequate psychological support mechanisms, emergence of psychiatric disorders can lead to deterioration and impaired functioning. As shown in many studies, intense stress and anxiety lead to weakness in the immune system and can lead to healthcare professionals becoming infected quickly during the outbreak.[6,7]

Protecting the mental health of healthcare workers involved in the pandemic is important. Through this, mental disorders may be prevented before they occur. Development of protective psychosocial support mechanisms through advance knowledge of the risk groups among healthcare workers is essential for the protection of public health.

Emergency department workers serve patients who have not yet been diagnosed. In addition, they have more contact with patients in terms of diagnosis and treatment. Workers in COVID-19 clinics serve diagnosed patients and their contact with patient is more limited than that of emergency workers. Therefore, there is a need to investigate the difference in anxiety situation between these two groups of workers.

OBJECTIVE

The aim of this study was to examine psychiatric disorders such as anxiety, depression and sleep disorder among healthcare professionals working in an emergency department and in a COVID-19 clinic.

METHODS

This research was started after approval had been obtained from the clinical research ethics committee of the training and research hospital of a local health sciences university (date: March 13, 2020; number: 449).

The study subjects were healthcare professionals in the emergency department and other units serving patients with COVID-19, in a training and research hospital in Turkey. The effect of interventions made among COVID-19 patients with exact diagnoses was assessed in relation to two groups of healthcare professionals. The primary group consisted of the emergency department medical team, which performs interventions without knowing their patients' diagnoses. The secondary group consisted of the healthcare team that provides care for hospitalized patients whose clinical, imaging and serological diagnoses have been made by infectious disease and chest disease specialists.

Our intention was to reach all employees in the emergency department. Therefore, all emergency service workers who agreed to participate in the study were included. The comparison group was selected from among employees in the COVID-19 clinic who presented similar sociodemographic characteristics. After forming the groups, 210 volunteers (105 primary and 105 secondary group employees) were included in the study after their consent had been received. The participants included physicians, nurses, data-entry staff, patient transportation staff, and patient support staff. At the time of forming the groups, these professionals were divided into three groups: physicians, nurses and other medical staff. Twelve participants were found not to have filled out the questionnaires appropriately and were excluded from the research. Thus, data from 198 volunteers were included in the study.

A sociodemographic data form and the Hospital Anxiety Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), World Health Organization Quality Of Life scale (WHOQOL-BREF-TR) and Religious Orientation Scale were applied to the volunteers.

Hospital Anxiety and Depression Scale (HADS): This scale, developed by Zigmond and Snaith[8] contains a total of 14 items. Seven questions on the scale assess anxiety and seven assess depression. The scale consists of four-point Likert-type questions, which are filled out by the individuals surveyed. On both the anxiety and the depression subscales, a score of 11 and above indicates a severe condition.

Pittsburgh Sleep Quality Index (PSQI): This scale, developed by Buysse et al.[9] in 1989, is the most widely used scale among sleep disorder-specific scales. Seven subscales are evaluated, with a total of 18 questions in the complete PSQI. These seven subscales relate to subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime sleep dysfunction. The response to each item is scored from 0 to 3, according to the frequency of symptoms. Higher values indicate poorer quality of sleep and higher levels of sleep disturbances. In this study, all the subscales of the PSQI were addressed.

World Health Organization Quality of Life scale (WHOQOL-BREF-TR): This was developed by the World Health Organization (WHO) for subjective evaluation of quality of life.[10] The aim of the scale items is to investigate the quality of life in five domains. These five domains relate to physical, mental, social, environmental and general health. Higher scores indicate higher quality of life.

Religious Orientation Scale: The religious orientation scale (ROS), developed by Allport and Ross, is composed of five-point

Likert-type items.[11] The scale is divided into three subscales: intrinsic religious orientation, extrinsic-personal religious orientation and extrinsic-social religious orientation. Higher scores on the scale indicate greater significance of the relevant subscale. A high score from a given subgroup means that belief within that subgroup (for example, internal religious orientation) is high.

Statistical evaluation

The data were analyzed using the SPSS 16.0 software package (SPSS Inc, Chicago, United States). Analysis on the categorical data was performed using the chi-square test. Student's t test was used in binary groups of analysis on quantitative data. Covariance analysis was applied to the variables, which were deemed statistically significant according to the results from the logistic regression analysis.

Logistic regression analysis was performed to determine the risk factors for severe development of anxiety and depression. Firstly, single-variable logistic regression analysis was performed for all the data obtained in the study. Following this, the variables with $P < 0.05$ were subjected to multivariate logistic regression analysis, as covariance factors. A statistical significance level of $P < 0.05$ was used in all analyses.

RESULTS

In the analysis on the sociodemographic data, there were no statistically significant differences between the groups (**Table 1**).

Among the HADS scores, it was noteworthy that a high number of the participants scored 11 and above, which was indicative of the presence of severe anxiety and depression. The anxiety and depression subscale scores were above 11 points for 39.4% and 31.3%

Table 1. Comparison of categorical and numerical sociodemographic data between the groups

	Emergency team (n = 100)n (%) or mean ± SD	Other teams (n = 98) n (%) or mean ± SD	χ^2	P
Gender				
Female	42 (53.8)	36 (46.2)	0.448	0.2
Male	58 (48.3)	62 (51.7)		
Marital status				
Single	28 (43.8)	36 (56.3)	0.189	0.2
Married	72 (53.7)	62 (46.3)		
Profession				
Physician	34 (53.1)	30 (46.9)		
Nurse	29 (40.8)	42 (59.2)	4.53	0.1
Other	37 (58.7)	26 (41.3)		
Living arrangements				
Living with parent	24 (48.0)	26 (52.0)		
Living with spouse and children	66 (53.2)	58 (46.8)	1.262	0.7
Sharing a bachelor apartment	4 (40.0)	6 (60.0)		
Living alone	6 (42.9)	8 (57.1)		
Chronic disease				
Yes	14 (45.2)	17 (54.8)	0.517	0.3
No	86 (51.5)	81 (48.5)		
Diagnosis of the disease				
Hypertension	5 (45.5)	6 (54.5)		
Diabetes mellitus	1 (33.3)	2 (33.3)	0.517	0.9
Other	9 (52.9)	8 (47.1)		
HADS severity of anxiety				
Marked severity	60 (60.0)	18 (18.4)	35.93	< 0.001
Borderline or normal	40 (40.0)	80 (81.6)		
HADS severity of depression				
Marked severity	51 (51.0)	11 (11.2)	36.40	< 0.001
Borderline or normal	49 (49.0)	87 (88.8)		
Age (years)	35.2 ± 6.4	33.71 ± 7.2		0.1
Number of children	1.34 ± 1.2	1.04 ± 1.05		0.07
Length of education (years)	14.05 ± 2.9	14.38 ± 2.7		0.4
Professional experience (years)	10.2 ± 6.5	9.4 ± 6.9		0.4
Length of time working in the unit (years)	4.8 ± 4.2	4.6 ± 4.5		0.7

HADS = Hospital Anxiety and Depression Scale; HADS anxiety of marked severity = anxiety subscale score of 11 and above on HADS; HADS depression of marked severity = depression subscale score of 11 and above on HADS; SD = standard deviation.

of these individuals, respectively. From the perspective of primary and secondary encounters with potential COVID-19 patients, it was found that the scores on the anxiety and depression subscales were both significantly higher in the group that was facing potential COVID-19 cases first (P < 0.001; **Table 1**).

It was observed that both the anxiety and depression HADS scores were significantly higher among emergency staff (**Table 2**).

The perceived stress levels and PSQI subscale scores of the participants in the primary group were significantly higher than those of participants in the secondary group (P < 0.001, **Table 2**).

The risk of developing anxiety in the female gender was found to be 16.6 times greater than in males. In addition, the relative risk for anxiety development was 8.7 times higher in physicians and 4.8 times higher in nurses when compared with other professional groups (**Table 3**).

In the multivariate logistic regression analysis, gender, profession, HADS-depression, the use of sleeping medication subscale score of the PSQI, the perceived stress level and the WHOQOL physical and environmental domain subscale scores were found to be the effective risk factors (**Table 4**).

There were significant differences in the HADS, PSQI and WHOQOL subscale scores between the primary group and the secondary group. On the other hand, while the Religious Orientation Scale score was higher in the primary group, this difference was not statistically significant.

Table 2. Statistical analysis on the scores for the scales that were applied to the groups

	Emergency team (n = 100) Mean ± SD	Other teams (n = 98) Mean ± SD
Religious orientation – intrinsic orientation	41.2 ± 6.7	40 ± 6.3
Religious orientation – external personal orientation	24.2 ± 5.3	23.9 ± 5.1
Religious orientation – social religious orientation	13.7 ± 4.4	12.7 ± 4.5
HADS anxiety score**	12 ± 4.5	7 ± 3.4
HADS depression score**	10.8 ± 4.4	6.4 ± 3
PSQI subjective sleep quality**	1.58 ± 0.8	1.1 ± 0.6
PSQI time to fall asleep**	1.8 ± 0.9	1.1 ± 0.9
PSQI sleep duration*	1.1 ± 1	0.7 ± 0.8
PSQI habitual sleep efficiency	0.5 ± 0.9	0.3 ± 0.7
PSQI sleep disturbances	1.5 ± 0.7	1.4 ± 0.9
PSQI use of sleep medication**	0.2 ± 0.5	0.4 ± 0.1
PSQI daytime dysfunction **	1.47 ± 0.9	0.6 ± 0.7
Perceived stress level score**	28 ± 10.6	17.7 ± 7.1
WHOQOL overall health**	5.5 ± 1.5	6.4 ± 1.7
WHOQOL physical health**	22.2 ± 4.6	25.5 ± 4.7
WHOQOL psychological health**	19.3 ± 4.2	21.8 ± 3.7
WHOQOL social relation**	9.5 ± 2.2	11.2 ± 3.3
WHOQOL environmental health**	22.9 ± 5.3	25.6 ± 5.4

SD = standard deviation; HADS: Hospital Anxiety and Depression Scale; PSQI = Pittsburgh Sleep Quality Index; WHOQOL: World Health Organization Quality Of Life scale; * = P < 0.01; ** = P < 0.001.

DISCUSSION

The HADS scores of all the participants in this study showed that a high number of them scored 11 and above, which is indicative of the presence of severe anxiety and depression. The anxiety and depression scale scores were above 11 points for 39.4% and 31.3% of these individuals, respectively. From the perspective of primary and secondary encounters with potential COVID-19 patients, it was found that the scores on the anxiety and depression subscales were both significantly higher in the group that faces potential COVID-19 cases first. This indicates that staff in the primary group, i.e. those involved in the emergency unit, which is the place to which these patients are first admitted, are at higher risk of anxiety and depression. We believe that the higher values for the scores on these scales may have been due to the examinations and interventions that were performed on these patients before their diagnoses had become established. These higher values may also have been due to the working conditions of the emergency department, which are more stressful than those of other work areas.

In a study on emergency physicians, Wong et al. reported that these physicians' scores on the anxiety and perceived stress scales were higher than those of other physicians.[12] In the present study, stress levels and stress-related anxiety levels were significantly higher among emergency staff, in line with the literature. In another study, González-Cabrera et al.[13] compared anxiety and salivary cortisol levels among the emergency service staff on normal days and on shift days. They found that emergency service employees had higher anxiety and salivary cortisol levels. Similarly, the higher levels of anxiety and stress found among the emergency service employees in our study support the hypothesis that changes to cortisol levels may have occurred in the same manner as reported in the previous study. Moreover, this may occur in association with immune system defects.

Stress, which can play a role in the etiology of numerous psychiatric disorders, can be considered to be a symptom of psychiatric disorders. In addition, stress can be both the cause and the result of sleep disorders. The response of the body against stress aims to provide the necessary homeostasis for the survival of life.

Many hormonal and neuronal mechanisms may play a role in this homeostasis. One of these mechanisms is the hypothalamic-pituitary-adrenal (HPA) axis. Sleep quality is among the parameters associated with the layout of the HPA axis.

Cortisol is a stress hormone with significant effects on the immune system. It has the capacity to cause serious immune disorders, depending on its secretion level.[14] The perceived stress levels and PSQI subscale scores of the members of the primary

group in the present study were significantly higher than those of the secondary group.

These high levels of stress and the deterioration of sleep quality among healthcare professionals during the pandemic need to be highlighted. Their immune systems are at a low ebb at these times, which means that these individuals can become infected quickly. If this happens, the healthcare system will suffer loss of functionality.

Table 3. Statistical differences in the scores for the scales, according to profession

	Physician (n = 61) Mean ± SD or n (%)	Nurse (n = 71) Mean ± SD or n (%)	Other (n = 63) Mean ± SD or n (%)	Total n %
Sex				
Female	14 (17.9)	30 (38.5)	34 (43.6)	78 (100)
Male	50 (41.7)	41 (34.2)	29 (24.2)	120 (100)
Age	34.81 ± 7.66	34.3 ± 6.83	34.43 ± 6.17	
HADS anxiety score***	7.63 ± 3.7	10.1 ± 4.8	10.8 ± 4.8	
HADS depression score***	7.2 ± 4.1	9.1 ± 4.5	9.5 ± 4.1	
Intrinsic religious orientation***	37 ± 6.9	42 ± 6.3	42.7 ± 4.4	
Personal-extrinsic religious orientation***	21.2 ± 5.3	24.3 ± 5.2	26.7 ± 3.4	
Social religious orientation***	10.6 ± 3.5	13.1 ± 4	16 ± 4	
PSQI subjective sleep quality	1.2 ± 0.7	1.3 ± 0.7	1.4 ± 0.8	
PSQI time to fall asleep**	1.1 ± 0.9	1.7 ± 1	1.4 ± 0.9	
PSQI sleep duration	0.7 ± 0.7	0.9 ± 1	1.1 ± 1	
PSQI habitual sleep efficiency**	0.1 ± 0.3	0.4 ± 0.9	0.6 ± 1	
PSQI sleep disturbances***	1.1 ± 0.7	1.6 ± 0.8	1.7 ± 0.7	
PSQI use of sleep medication	0.1 ± 0.5	0.1 ± 0.5	0 ± 0.1	
PSQI daytime dysfunction	0.9 ± 1	1.1 ± 0.9	1.1 ± 0.8	
Perceived stress level score***	18.6 ± 8.3	23.6 ± 10.6	26.5 ± 10.6	
WHOQOL overall health	6.3 ± 1.4	5.7 ± 1.8	5.8 ± 1.6	
WHOQOL physical health*	25.1 ± 3.9	22.7 ± 5.2	24 ± 5.3	
WHOQOL psychological health	21.2 ± 3.8	20.5 ± 4.3	19.8 ± 4.2	
WHOQOL social relation*	10.8 ± 2.1	10.6 ± 3.8	9.6 ± 2.2	
WHOQOL environment***	27.8 ± 3.9	23.3 ± 5.5	21.7 ± 5.2	

SD = standard deviation; HADS = Hospital Anxiety and Depression Scale; PSQI = Pittsburgh Sleep Quality Index; WHOQOL: World Health Organization Quality Of Life scale; *P < 0.05; **P < 0.01; ***P < 0.001.

Table 4. Multivariate logistic regression analysis results

	95% confidence interval		Odds ratio	P
	Lower	Upper		
Gender (female)	0.015	0.237	16.631	**< 0.001**
Profession (other)	1.110	37.142	1	0.147
Profession (physician)	1.370	55.877	8.750	**0.022**
Profession (nurse)	1.036	22.667	4.845	**0.045**
Working unit (primary)	0.660	13.058	1.998	0.158
Intrinsic religious orientation	0.938	1.272	1.290	0.256
Personal-extrinsic religious orientation	0.956	1.376	2.181	0.140
HADS-depression	1.131	1.771	9.194	**0.002**
PSQI subjective sleep quality	0.742	4.560	1.734	0.188
PSQI time to fall asleep	0.911	3.373	2.824	0.093
PSQI sleep duration	0.411	1.783	0.172	0.679
PSQI sleep disturbances	0.411	3.022	0.046	0.831
PSQI use of sleep medication	1.402	14.838	6.357	**0.012**
PSQI daytime dysfunction	0.463	2.452	0.022	0.882
Perceived stress level	1.050	1.278	8.639	**0.003**
WHOQOL overall	0.940	2.962	3.062	0.080
WHOQOL physical	1.072	1.764	6.299	**0.012**
WHOQOL psychological	0.737	1.221	0.167	0.683
WHOQOL social	0.574	1.174	1.165	0.280
WHOQOL environmental	0.640	0.939	6.757	**0.009**

HADS = Hospital Anxiety and Depression Scale; PSQI = Pittsburgh Sleep Quality Index; WHOQOL = World Health Organization Quality Of Life scale.

Studies have shown that attention and decision-making mechanisms are affected in situations of psychiatric disorders, such as anxiety disorder and depressive disorder. Moreover, it has also been reported that stress has negative effects on attention.[15,16]

Healthcare professionals use their higher cortical functions when making diagnoses and planning treatments. Any mistake made at such times can cause the loss of the patient. Thus, in situations of anxiety, high stress and depression, in which the higher cortical functions are affected, healthcare professionals are more likely to make mistakes.

In order to correct this condition, it is necessary to eliminate the causes that pose the risk. In the present study, HADS-depression, HADS-anxiety and stress level test scores were higher among the primary healthcare professionals than among the secondary healthcare professionals. Considering that increased anxiety, depression and stress levels negatively affects cortical functions, it can be stated that lowering these scores effectively will be a very important factor in preventing transmission of the disease to healthcare professionals. For this reason, systematic support programs for healthcare professionals, including pharmacotherapy options, need to be developed quickly.

Quality of life can be impaired for any reason that affects physical and mental health. In the present study, the negative changes in quality of life detected through WHOQOL were consistent with reports in the literature showing that quality-of-life scale scores were low among patients with high depression scale scores.[17,18]

The most likely behavior among healthcare professionals, who know that higher burdens of the virus are a negative factor regarding the prognosis, is to keep their contact and communication with their patients at a minimum level, when they meet these patients after admission to the emergency service, for diagnosis and treatment planning. This can be considered to be an instinctive action by professionals to protect themselves. However, it should be noted that fear and anxiety may increase in patients who are already fearful upon admission to the emergency service, as a result of such behavior among healthcare professionals.

If patients are unable to learn the basic information that needs to be learned, such as the diagnosis of the disease, its severity and the duration of the treatment to be administered, they will be more likely to be affected mentally. Conversely, healthcare professionals who do not want to be exposed to the burden of the virus will feel guilty if they fail to inform their patients adequately, given that they will think that they are not adhering to the ethical rules. Healthcare professionals are trapped between, on the one hand, their fear of becoming ill and infecting their family members, which should be seen as normal human behavior; and, on the other hand, the idea that they might not be able to properly inform their patients in an ethical manner. Thus, it should be noted that healthcare professionals constitute an at-risk group for psychiatric disorders in the future.

In the present study, logistic regression analysis was used to determine the risk factors that led to severe HADS scores. Parameters that were found to be significant in univariate logistic regression analysis were included as covariance factors in multivariate logistic regression analysis. Gender, profession, HADS-depression, the use of sleeping medication parameter of the PSQI, perceived stress and the WHOQOL physical and environmental subscale scores were found to be the effective risk factors.

In this study, the risk of developing anxiety among females was found to be 16.6 times greater than among males. In addition, the relative risk of developing anxiety was 8.7 times higher among physicians and 4.8 times higher among nurses than in other professional groups. Higher rates of anxiety and depression among women are an accepted fact.[19] We believe that these higher rates among women are caused by a pandemic-specific fear of losing a spouse, child or relative, or of infecting relatives with the virus. Among the healthcare professionals, physicians and nurses (who have higher levels of education and experience) were found to have higher risk values. This suggests that physical proximity and longer contact time with COVID-19 patients are more likely to be effective for development of anxiety, rather than the respective knowledge. However, considering the data available in the medical world regarding this disease, it remains true that people in these professions are not knowledgeable enough. Greater knowledge about this disease will decrease the concerns among professionals such as physicians and nurses.

The relative risk of developing anxiety, regardless of the groups, was found to be 9.1 times higher for the HADS-depression variable, 6.3 times higher for the use of sleeping medication parameter of the PSQI, 8.6 times higher for the perceived stress level score and 6.2 and 6.7 times higher for the WHOQOL physical and environmental factors, respectively. Coexistence of depression and anxiety has been the subject of numerous studies.[20,21] In cases of higher anxiety, deterioration in sleep quality is an expected risk, especially during an extraordinary period, such as the current pandemic. It can be expected that sleep disturbances for which sleeping medication is required will show scientifically proportionate correlations with the severity of anxiety. A high level of perceived stress may be one of the indicators of high levels of anxiety. There are other studies with the same results in the literature.[22,23] In parallel, quality of life is severely affected in all cases of psychiatric or physical disorders, and this is reflected in the scores on scales that measure the quality of life.

In summary, the pandemic has led to anxiety among healthcare workers. This anxiety was found to be higher among females in all three groups (doctors, nurses and other healthcare workers) than among males. There may be multiple reasons for this higher incidence among females. In the general population, high incidence of anxiety disorders among females may be explained by their concerns, as mothers and wives, about infecting relatives with the

disease and about the lack of adequate information regarding the course of the disease and future morbidity. The predominance of females among nurses may be the cause of the high level of anxiety within the nursing profession.

Limitations

This study was limited by its relatively small sample size and low response rate, and because it was conducted at a single academic medical center at one point in time. Therefore, these findings may lack generalizability. Further studies in this field are required, in order to make more confident assessments. This study was also subject to the limitations of the tests that we used.

CONCLUSION

Healthcare professionals on the frontline need systematic regular psychosocial support mechanisms. Anxiety due to fear of infecting family members can be prevented through precautions such as isolation. However, it should be remembered that loneliness and feelings of missing family members consequent to isolation may increase the risk of depression.

In summary, the pandemic has led to anxiety among healthcare workers. For this reason, systematic support programs for healthcare professionals, including pharmacotherapy options, need to be developed quickly.

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Address for correspondence:
Songül Araç
Department of Emergency Medicine, University of Health Sciences, Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Üçkuyular Mevkii 21070, Diyarbakır, Turkey
Tel. (+90) 5536848621
E-mail: drsongularac@gmail.com

Study of ongoing registered clinical trials on COVID-19: a narrative review

Md Insiat Islam Rabby[I], Farzad Hossain[II]

Islamic University of Technology, Gazipur, Bangladesh, and Universiti Putra Malaysia, Seri Kembangan, Selangor, Malaysia

[I]BSc, Engineer and Master's Student, Department of Mechanical and Manufacturing Engineering, Universiti Putra Malaysia, Seri Kembangan, Selangor, Malaysia.
orcid.org/0000-0003-0431-6101

[II]BSc, Engineer and Master's Student, Department of Mechanical and Production Engineering, Islamic University of Technology, Gazipur, Bangladesh.
orcid.org/0000-0001-8256-8553

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Biological.

ABSTRACT

BACKGROUND: The dangerous SARS-CoV-2 virus first emerged in China in December 2019 and has rapidly spread worldwide. Currently, it has affected more than 2,850,000 people. No vaccine or drug is available yet, and therefore researchers and scientists are striving to identify potential drugs or vaccines for combating this virus. We were unable to find any review of the literature or analysis on ongoing registered clinical trials that reported diagnostic tests, therapeutics, vaccines and devices for COVID-19 along with estimated enrollment, participants' ages, study type, start and completion date, status, treatment/intervention and country.

OBJECTIVE: To review ongoing trials relating to COVID-19.

METHODS: A systematic search for clinical trials was conducted in the ClinicalTrials.gov database up to April 12, 2020. A total of 339 trials relating to COVID-19 were analyzed and key information on each trial was recorded.

RESULTS: Most of the trials were being conducted in the United States and completion of most of them was expected by May 2020. They were mostly on drugs and treatment, while a minority were on diagnostic tests. The analysis showed that hydroxychloroquine was investigated in most of the trials. The trials identified were categorized into five classes: a) diagnostic tests; b) therapeutics; c) biologics and vaccines; d) devices and products; and e) others.

CONCLUSION: The trials identified have potential against COVID-19 that can be applied in treatment processes after the necessary investigations and experiments. Additionally, the items identified were organized in a proper way, which can assist in current research activities.

INTRODUCTION

The novel coronavirus (SARS-CoV-2) originated from Wuhan, in Hubei Province, China, and it has spread across more than 28 countries with more than 25,000 confirmed cases and around 500 deaths from mid-December 2019 to early February 2020.[1] Within that period, the case-fatality rate was around 2% and over 90% of the deaths and cases were in China.[1] Moreover, the majority of them were males with an average age of 55 years, according to reports on the initial surge of cases in Wuhan, which were linked to the Huanan Seafood Wholesale Market.[2] Almost similar symptoms (i.e. coughing, fever, myalgia and fatigue) were reported in most of the cases.[3] Pneumonia and some other serious and even fatal respiratory diseases (i.e. acute respiratory distress syndrome) were developed in the majority of the cases.[3]

The 2019 novel coronavirus (SARS-CoV-2) is a beta coronavirus and it forms a clade within the subgenus Sarbecovirus of the subfamily Orthocoronavirinae.[4] Outbreaks of some other beta coronaviruses of zoonotic origin, i.e. Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) occurred previously, in 2012 and 2003 respectively, and were linked to potentially fatal illness.[5,6] Around 3% pathogenicity has been observed in relation to SARS-CoV-2 according to the current evidence and this is comparatively lower than the rates for MERS-CoV (40%) and SARS-CoV (10%).[7] However, potentially higher transmissibility (R0: 1.4-5.5) has been observed for SARS-CoV-2, whereas it was only (R0: < 1) and (R0: 2-5) for MERS-CoV and SARS-CoV respectively.[7]

SARS-CoV-2 has the possibility of expansion globally and the World Health Organization has already declared it to be a Public Health Emergency of International Concern.[8] In this situation, rapid diagnostics, drugs and vaccines have become urgent necessities for promptly detecting, preventing and containing SARS-CoV-2. Potential quick diagnostics, drugs and vaccines

for SARS-CoV-2 have been described and assessed in systematic reviews. A few studies on clinical trials relating to COVID-19 (the disease that the novel coronavirus causes) are already in the literature, but these are not enough, given the current situation. These trials only focused on drugs and were also limited to specific regions.[9-12] No clinical trials on diagnostic tests, devices, vaccines, biologics, behavior and other matters have yet been reported in the literature. The present study identified and discussed all potential categories of registered clinical trials on COVID-19 in ClinicalTrials.gov database up to April 12, 2020. Additionally, statistical analysis based on the findings was also conducted.

OBJECTIVE

To create a complete study focusing on all categories of clinical trials relating to COVID-19, which is a necessity for assisting the current COVID-19 research activities.

METHODS

The necessary data were collected by searching ClinicalTrials.gov database up to April 12, 2020, using the descriptor [coronavirus] in the simple search field "conditions or disease", without restrictions on languages, disease conditions, results or locations. The details of the search strategy are shown in **Table 1**. Our search also included trials that were shown with the status "recruiting" and "not yet recruiting". On the other hand, trials for which the status was shown as "enrolling by invitation", "active, not recruiting", "suspended", "terminated", "completed", "withdrawn" or "unknown" were not included in this study.

Thus, every trial was defined in terms of its specific identification number, estimated enrollment, participants' ages, study type, start and completion date, status, treatment/intervention and country. From the information available in the database, we recorded and compared the continents of the clinical trials, total numbers of trials in various countries, expected completion time of the trials, phase of the trials, trial status, study type of the trials, estimated enrollment of participants in the trials, participants' ages and types of intervention or treatment used in the trial. We also analyzed the registered diagnostic tests, drugs, biologics and vaccines, devices and products, and behavioral and other clinical trials relating to COVID-19.

RESULTS

Currently, there are no specific remedies or vaccines for COVID-19 infection. Therefore, over the past few months, a huge number of clinical trials have been registered in the ClinicalTrials.gov database with the aim of identifying the most effective treatment and vaccine for COVID-19. This number is increasing continuously.

Our search in ClinicalTrials.gov identified 339 clinical trials on COVID-19. **Figure 1** shows the continents on which these trials were conducted. From this, it was observed that the largest proportion of the clinical trials (37%) were registered in Europe, while a minority (2%) were registered in Australia.

Figures 2A and **B** exhibit the range of the total numbers of trials among different countries. From these figures, it can be seen that the highest number of clinical trials (76) was registered in the United States and the second highest number (66) was registered in China. Meanwhile, only one trial was registered from Pakistan, Saudi Arabia, Jordan, Poland, Vietnam, Singapore, Romania, Guyana, Thailand, South Africa, Monaco, Argentina, Czech Republic, Hungary and Cyprus.

Figures 3A, **B**, **C** and **D** show the expected completion dates of the trials. The data show that the completion dates for these trials ranged from April 2020 to approximately the year 2030. It was observed that the largest proportion of these trials (36) were expected to be completed by May 2020. However, most of these trials were expected to finish by December 2021 and more than 200 trials were expected to finish by December 2020. Some trials were expected to finish in 2025 or 2026, and there was one trial that was supposed to be completed by March 2030, relating to "observation of behavior and COVID-19 infection". Therefore, the world

Table 1. Search strategy

#1 MeSH descriptor: [coronavirus] explode all trees = 280
#2 (COVID-19) OR (SARS-CoV) = 607
#3 #1 OR #2 = 887
Filters: in Trials Review; in *Title, Status, Interventions, Conditions* = 339

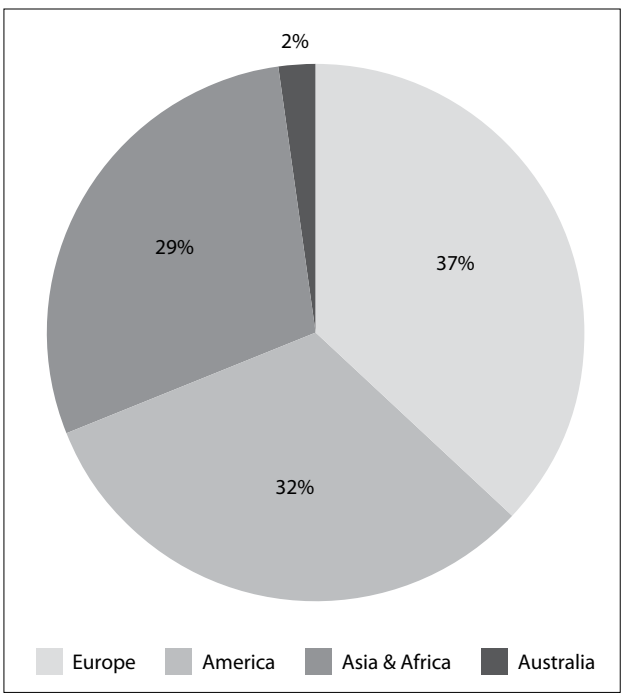

Figure 1. Continents of the clinical trials on COVID-19.

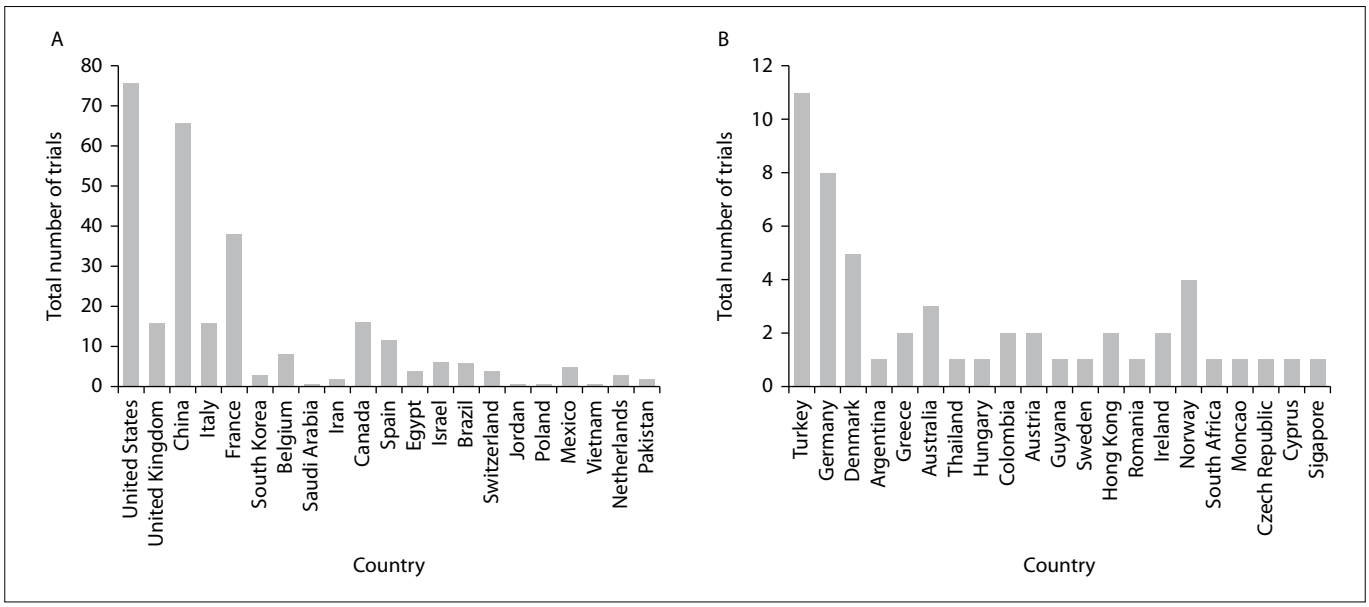

Figure 2. A. Total number of trials in various countries; B. Total number of trials in various countries (Continuation).

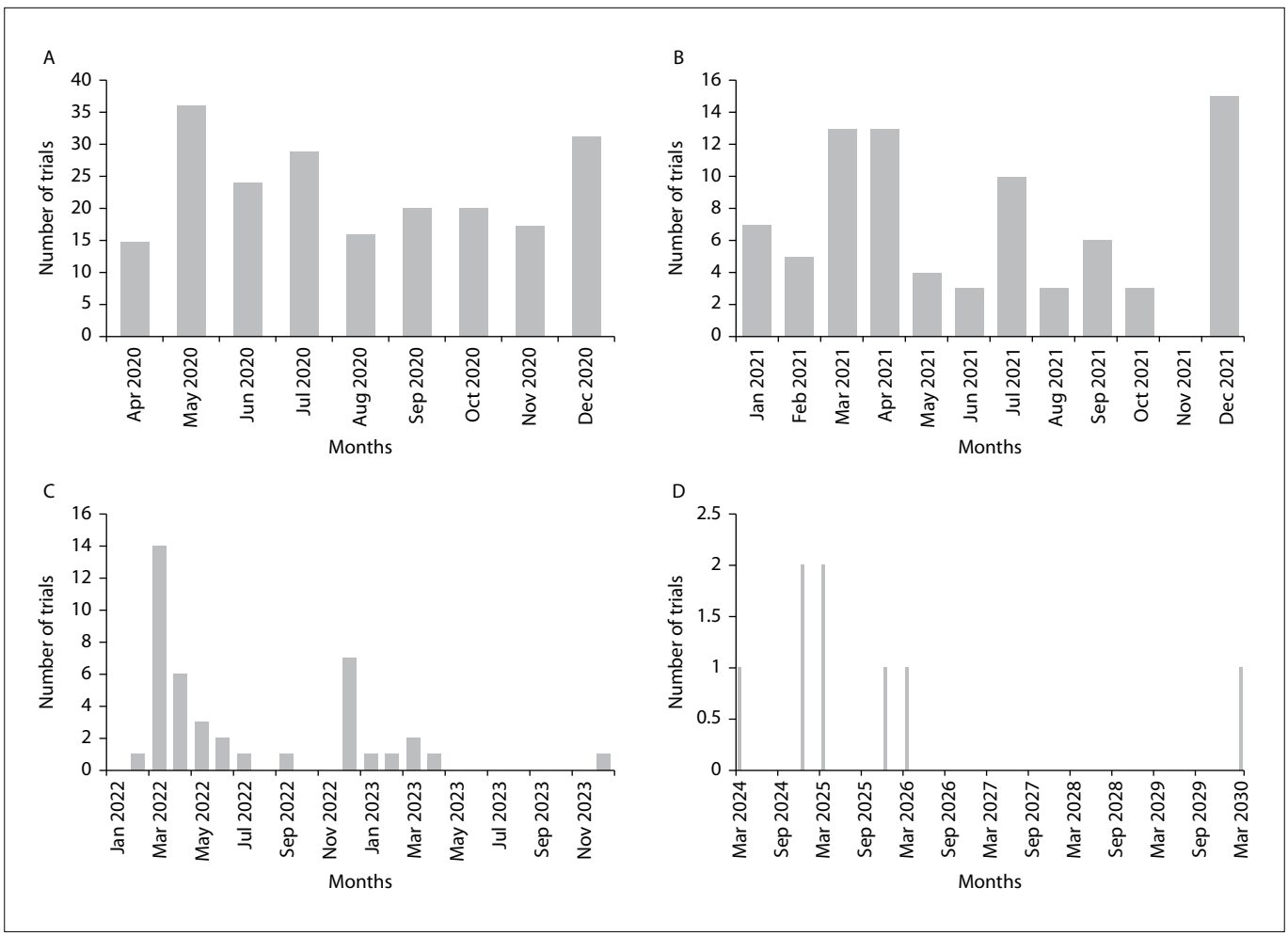

Figure 3. A. Expected completion dates of trials in 2020; B. Expected completion dates of trials in 2021; C. Expected completion dates of trials in 2022 and 2023; D. Expected completion dates of trials from 2024 to 2030.

still needs to wait for a certain time period, for effective results to be reached from these registered trials.

It was observed regarding the trial phase that the largest proportion of them (33%) related to phase 2, while a minority (4%) related to early phase 1. It was found from the trial status that most of them (56%) were not yet recruiting, while a minority (44%) were already recruiting. It was observed regarding the study type that most of the trials (73%) were interventional, while a minority (27%) were observational. It was found from the estimated enrollment of participants in the trial that most of the trials (46%) were planned to have enrollment of less than 500, but greater than or equal to 100. On the other hand, a minority (11%) were planned to have enrollment greater than or equal to 1000. It was observed from the participants' ages that most of the participants (85%) were within the '18 years and older' category whereas a minority (1%) were within the 'up to 18 years old' category. Using categories of intervention or treatment, the trials could be categorized into five classes: a) diagnostic tests; b) therapeutics; c) biologics and vaccines; d) devices and products; and e) others. In addition, it was observed from the categories of intervention or treatment that most of the trials (56%) were related to therapeutics (drugs and treatment), while a minority of the trials (7%) were related to diagnostic tests.

Diagnostic tests

According to the United States Centers for Disease Control and Prevention, specimens should be collected by healthcare professionals not only from the lower respiratory tract (through either bronchoalveolar lavage or an endotracheal tube) but also from the upper respiratory tract (either oropharyngeal or nasopharyngeal). The diagnosis of COVID-19 pneumonia is mainly dependent on RT-PCR investigation on specimens. Serological tests can be considered if RT-PCR is unavailable.

A commercial qualitative testing system for SARS-CoV-2 using the cobas® system (Roche, Basel, Switzerland) has now been approved by the United States Food and Drug Administration (FDA). The test needs samples from oropharyngeal or nasopharyngeal swabs, and the result can be obtained within 3.5 hours. The cobas® SARS-CoV-2 test is a kind of double target assessment test depending upon the RT-PCR methodology. It can detect not only the particular SARS-CoV-2 ribonucleic acid but also the extremely conserved part of the invariant E gene in every member of the Sarbecovirus subgenus. To ensure accuracy and specificity, the assay comprises a comprehensive process with internal control, positive control and negative control.

Moreover, permission for urgent use of the Xpert Xpress SARS-CoV-2 test (Cepheid Inc, California, United States) was granted by the United States Food and Drug Administration (FDA) on March 21, 2020. This is another qualitative test, from which results can be obtained within 45 minutes. Whenever more than one targeted gene is detected, the results should be treated as positive. At present, the screening methods depend upon appearance of plenty of viral genomes at the sample collection site. Studies have revealed that high levels of immunoglobulin M antibodies were present in both subclinical and symptomatic patients, five days after the onset of illness. Therefore, to enhance the sensitivity of detection, combination of the polymerase chain reaction and the immunoglobulin M enzyme-linked immunosorbent assay has been proposed.[13]

However, to facilitate the diagnostic process relating to COVID-19, 25 clinical trials have been registered in the ClinicalTrials.gov database as diagnostic tests, and these are shown in **Table 2**.[14] These trials described diagnostic tests focusing on an immunoglobulin G

Table 2. Diagnostic tests for COVID-19 registered in clinical trials

Diagnostic test	Number of trials	Remarks
Breath test	1	This consists of noninvasive detection of pneumonia in the context of COVID-19 using gas chromatography.[14]
Data collection and rhinopharyngeal swab	1	Testing for SARS-CoV-2 and other respiratory pathogens by PCR via nasopharyngeal swabbing and IgM/IgG rapid serological tests.[14]
Electrocardiogram and transthoracic echocardiography	1	Systematic collection of cardiovascular data to study the incidence of myocarditis and coronaropathy events during COVID-19 infection.[14]
COVID-19 diagnostic test	1	This has the aim of comparing three tests: PCR, an antigenic rapid diagnostic orientation test (RODT) and a serological TROD.[14]
New QIAstat-Dx fully automatic multiple PCR detection platform	1	Automatic multiple PCR detection platform to test the enrolled patients.[14] The reasonably designed experiments are used to verify the performance of the cartridge detection and prove its clinical application value.[14]
Scanning chest X-rays and performing AI algorithms on images	1	To identify the radiographs of patients with COVID-19 and those with influenza pneumonitis, with accuracy verified through COVID-19 tests.[14]
Nasopharyngeal swab	2	To assess the prevalence and incidence of COVID-19 infection in patients with chronic plaque psoriasis who are on immunosuppressive therapy.[14]

Continue...

Table 2. Continuation

Diagnostic test	Number of trials	Remarks
COPAN swabbing* and blood sample collection	1	Used for immune protection and pathogenesis in SARS-CoV-2 and sampling can be delivered via existing research personnel from furloughed projects.[14]
Lung ultrasound	2	Used to diagnose the etiology of respiratory failure in a PICU.[14]
Thoracic CT scan	1	Used to evaluate the diagnostic performance of chest CT in screening for COVID-related lung injury.[14]
SARS-CoV-2 IgG antibody testing kit	2	An at-home fingerprick test for SARS-CoV-2 IgG antibodies, used for high-risk healthcare workers.[14]
Sampling salivary	1	Used to evaluate the performance of a detection test for diagnosing SARS-CoV-2.[14]
Titanium blood test	1	This is used to continue patient monitoring and identify those at greatest risk of implant-related issues in the absence of regular clinic visits.[14]
Electrocardiogram, telemetry, echocardiogram, laboratory values	1	These tests are done in order to identify cardiovascular manifestations of hospitalized patients with coronavirus disease 2019.[14]
Ultrasound lung imaging as part of FAST + evaluation	1	FAST adjunct evaluation in the trauma bay that can include lung parenchyma imaging at the initial assessment to help stratify patients into low or high-risk groups for active COVID-19 infection.[14]
Point-of-care ultrasonography (POCUS)	1	Used to analyze changes in the appearance of the lungs and heart through serial acquisition of focused point-of-care ultrasound images in a cohort of patients with or under investigation for COVID-19.[14]
Assessment of cardiovascular diseases and cardiovascular risk factors	1	Cardiovascular disease risk factors are defined as characteristics, both modifiable and non-modifiable, that increase the risk of developing CVD.[21] SARS-CoV-2 infects host-cells via ACE2-receptors and leads to myocardial injury and chronic damage to the cardiovascular system.[14]
SAMBA II (Diagnostic for the Real World)	1	SAMBA II provides a simple and accurate system for diagnosing infection with SARS-CoV-2.
Cambridge Validated Viral Detection Method	1	This is a modified PCR test method for diagnosing infection within four hours, which is much faster than the current tests.
Biomarker expression	1	Used for clinical diagnosis among patients who develop a flu-like syndrome with fever and coughing.[14]
Standard screening strategy and new screening strategy	1	Designed to compare the screen accuracy and efficiency of two screening strategies.[14]
Odd/even birth year intervention groups	1	Used to measure the agreement between the detection of SARS-CoV-2 virus using a foam nasal swab tested directly after collection.[14]
Radiological detection	1	Used to detect chest X-ray and CT scan of viral infection in the lungs.[14]
Serology	1	Serology is the scientific study of serum and other body fluids. It is used for diagnostic identification of antibodies in the serum.
Recombinase-aided amplification (RAA) assay	1	Recombinase-aided amplification (RAA) assay is a novel isothermal nucleic acid amplification technique that can detect a variety of pathogens.[14]

PCR = polymerase chain reaction; IgM = immunoglobulin M; IgG = immunoglobulin G; AI = artificial intelligence; CT = computed tomography; FAST = focused assessment with sonography for trauma; CVD = cardiovascular disease; ACE2 = angiotensin-converting enzyme 2; VTM = viral transport media; PICU = pediatric intensive care unit.
*COPAN ITALIA SpA, Brescia, Italy.

antibody testing kit to detect the virus, lung ultrasound to diagnose the etiology of respiratory failure in a pediatric intensive care unit and nasopharyngeal swabs to identify associated risk factors. Apart from these tests, breath tests, blood tests, computed tomography scans, serological tests, ultrasonography, radiological detection, electrocardiogram and transthoracic echocardiography, cell phone-based auto-diagnosis systems, scanning chest X-rays and use of artificial intelligence algorithms on images, etc., were registered in clinical trials focusing on several diagnostic tests to detect the virus, determine patients' health status and make risk assessments.

One trial is using the Cambridge Validated Viral Detection Method, which is a modified polymerase chain reaction (PCR) test method that makes it possible to diagnose infection within four hours, which is much faster than the current tests. Another trial that has been registered is working to compare three tests that are currently available: PCR, antigenic rapid diagnostic orientation test and serological rapid tests for diagnostic orientation. Most of these registered trials will be finished by the end of 2020 and the successful trials will be able to facilitate the diagnostic process for COVID-19 patients.

Therapeutics (drugs and treatment)

At present, COVID-19 pneumonia has no specific treatment. Therefore, the need for supportive care and preclusion of complications and nosocomial transmission has been emphasized by clinical managements. Oxygen should be provided as soon as possible to patients who experience respiratory distress. However, fluid replacement should be comparatively conservative unless there is any sign of hypoperfusion of tissue, since this can result in edema of the lungs and worsen the oxygen status. In addition, fluid replacement is an important concept within treatments for severe acute respiratory infections because of its ability to shorten the duration of ventilation. Systemic corticosteroids have the potential to delay clearance of viruses and so they are not generally recommended.

However, most of the drugs investigated in the present COVID-19 trials and treatments were basically designed for another bacterium. Several trials were started in order to test particular antibodies and vaccines, mainly targeting SARS-CoV-2. Here, these ongoing therapeutic options have been summarized.

Up to April 12, 2020, 188 clinical trials relating to for SARS-CoV-2 therapeutics had been registered in the clinical trials registry (ClinicalTrials.gov). These are reported in **Table 3**.[14]

Table 3. Drugs for treating COVID-19 identified in registered clinical trials

Drugs	Number of trials	Remarks	Drug category
Thalidomide	2	Thalidomide has immune regulatory effects.[14] Formula: $C_{13}H_{10}N_2O_4$	Anti-inflammatory
Naproxen	1	Used to treat pain and inflammatory diseases. Formula: $C_{14}H_{14}O_3$	Anti-inflammatory
Ibuprofen	1	Used to treat pain, fever, and inflammation. Formula: $C_{13}H_{18}O_2$	Anti-inflammatory
Escin	1	Used for treatment of chronic venous insufficiency. Formula: $C_{55}H_{86}O_{24}$	Anti-inflammatory
Piclidenoson	1	Used for autoimmune-inflammatory disorders. Formula: $C_{18}H_{19}IN_6O_4$	Anti-inflammatory
Colchicine	4	Colchicine lessens the building up of uric acid crystals. Formula: $C_{22}H_{25}NO_6$	Anti-inflammatory
CD24Fc	1	This is a biological immunomodulator. It addresses the major challenges associated with COVID-19.[14]	Anti-inflammatory
Aspirin	1	Used to reduce pain, fever, or inflammation. Formula: $C_9H_8O_4$	Anti-inflammatory
Hydrocortisone	1	Used as a replacement treatment for people whose adrenal glands are not producing enough natural cortisol.[14] Formula: $C_{21}H_{30}O_5$	Anti-inflammatory
ACE inhibitor	2	ACE inhibitors are used primarily for treatment of high blood pressure and heart failure.	Anti-inflammatory
Hyperbaric oxygen	1	Shows beneficial effects in various inflammatory diseases.[14]	Anti-inflammatory
Nitric oxide	5	This stimulates the release of certain hormones, such as insulin and human growth hormone.	Anti-inflammatory
N-acetylcysteine + Fuzheng Huayu tablet	1	N-acetylcysteine is a part of basic treatment. Fuzheng Huayu tablets have been proved effective in inhibiting MMP activity, to protect the subepithelial basement membrane.[14]	Anti-inflammatory
N-acetylcysteine + Placebo	1	N-acetylcysteine is a part of basic treatment. Placebo is used in clinical trials to test the effectiveness of treatments.	Anti-inflammatory
NORS (nitric oxide releasing solution)	1	NORS has the potential to decontaminate the upper respiratory tract.[14]	Anti-inflammatory
Lopinavir/ritonavir tablets combined with Xiyanping injection	1	Lopinavir/ritonavir is a promising candidate for both COVID-19 treatment and PEP.[14] Xiyanping injection has anti-inflammatory and immune regulatory effects.	Anti-inflammatory
Darunavir	1	Used to treat and prevent HIV/AIDS. Formula: $C_{27}H_{37}N_3O_7S$	Antiretroviral
Immunoglobulin of cured patients	1	This acts as a critical part of the immune response by specifically recognizing and binding to antigens.[14]	Antiretroviral
Emtricitabine/tenofovir disoproxil	1	Used to treat HIV with a combination of two antiretroviral medications: tenofovir disoproxil and emtricitabine.	Antiretroviral
ASC09/ritonavir group	1	These are antiretroviral medications. A combination of them has been used for SARS-CoV-2 pneumonia.[14]	Antiretroviral

Continue...

Table 3. Continuation

Drugs	Number of trials	Remarks	Drug category
Ritonavir + oseltamivir	1	Ritonavir is used to treat HIV. This combination has been used for SARS-CoV-2 pneumonia.[14]	Antiretroviral
Lopinavir/ritonavir	15	Lopinavir has been used against HIV infections as a fixed-dose combination with another protease inhibitor, ritonavir. Formula: $C_{37}H_{48}N_6O_5S_2$	Antiviral
Arbidol	2	Arbidol is pharmacodynamic in vitro against coronaviruses. Formula: $C_{22}H_{25}BrN_2O_3S$	Antiviral
Favipiravir	3	It has low toxicity (CC50 > 400 μM).[22] Formula: $C_5H_4FN_3O_2$	Antiviral
Ribavirin	1	Used to treat hepatitis C and some viral hemorrhagic fevers. Formula: $C_8H_{12}N_4O_5$	Antiviral
Natural honey	1	Honey as a first-line treatment for acute cough caused by upper respiratory tract infection.[14]	Antiviral
Favipiravir combined with Tocilizumab	1	Favipiravir is used to treat influenza. Tocilizumab is used to treat rheumatoid arthritis.	Antiviral
Antiviral treatment and prophylaxis	1	The aim is to treat non-severe confirmed cases of COVID-19 and provide chemoprophylaxis for their contacts.[14]	Antiviral
Remdesivir	7	Nucleotide analog that inserts into viral RNA chains.	Antiviral
DAS181	5	This shows inhibitory activity against seasonal influenza.[23]	Antiviral
Placebo	39	A placebo is an inert substance or treatment that is designed to have no therapeutic value.	Other treatment/ drug
Remdesivir placebo	2	Remdesivir is a nucleotide analog. Placebo is used with this in order to test the effectiveness of treatments.	Antiviral
Oseltamivir	4	This inhibits viral neuraminidase.[24] Formula: $C_{16}H_{28}N_2O_4$	Antiviral
ASC09F + oseltamivir	1	Oseltamivir reduces the spread in the respiratory tract.[24] ASC09F has been combined with oseltamivir to evaluate efficacy in relation to SARS-CoV-2 pneumonia.[14]	Antiviral
Combination of protease inhibitors, oseltamivir, favipiravir, and chloroquine	1	Used for antiviral treatment, orally. They are intended to have a systemic effect, reaching different parts of the body.	Antiviral
Arbidol hydrochloride	2	Used to prevent severe pneumonia and cytokine dysregulation induced by influenza viruses. Formula: $C_{22}H_{26}BrClN_2O_3S$	Antiviral and anti-inflammatory
Lopinavir/ritonavir + hydroxychloroquine	2	Lopinavir/ritonavir is a promising candidate for COVID-19 treatment.[14] Hydroxychloroquine is used to prevent malaria in areas where malaria remains sensitive to chloroquine.	Antiviral and anti-inflammatory
Plaquenil	1	Used to prevent and treat malaria. Formula: $C_{18}H_{26}ClN_3O$	Antimalarial
Chloroquine analog (GNS651)	1	This has been tested in patients with advanced or metastatic cancer who have SARS-CoV-2 infection that is not eligible for a resuscitation unit.[14]	Antimalarial and anti-inflammatory
Hydroxychloroquine + azithromycin	2	These are antiviral plus anti-inflammatory and are used for improving the efficacy of eradication of COVID-19 virus.[25]	Antiviral and anti-inflammatory
Hydroxychloroquine	38	Hydroxychloroquine is a drug that has been used to improve the clinical outcome from COVID-19.[25] Formula: $C_{18}H_{26}ClN_3O$	Antimalarial and anti-inflammatory
Chloroquine	4	Chloroquine is a medication primarily used to treat malaria in areas where malaria remains sensitive to its effects. Formula: $C_{18}H_{26}ClN_3$	Antimalarial and anti-inflammatory
Chloroquine phosphate	4	Chloroquine phosphate is the phosphate salt of chloroquine with antimalarial and anti-inflammatory properties. Formula: $C_{18}H_{32}ClN_3O_8P_2$	Antimalarial and anti-inflammatory
Hydroxychloroquine sulfate	9	Hydroxychloroquine sulfate works by reducing inflammation in people with autoimmune diseases.	Antimalarial and anti-inflammatory
Siltuximab	2	Siltuximab is a chimeric monoclonal antibody. Formula: $C_{6450}H_{9932}N_{1688}O_{2016}S_{50}$	Antibody
Meplazumab for injection	1	This has the potential to mediate both treatment and prophylaxis of falciparum malaria.[14]	Antibody
Bevacizumab	2	This is an anti-VEGF recombinant monoclonal antibody. Formula: $C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$	Antibody
Nivolumab	1	This works as a checkpoint inhibitor.	Antibody

Continue...

Table 3. Continuation

Drugs	Number of trials	Remarks	Drug category
γ-globulin	1	A major class of immunoglobulins found in the blood.	Antibody
Mavrilimumab	1	Used to treat rheumatoid arthritis. Formula: $C_{6706}H_{10438}N_{1762}O_{2104}S_{54}$	Antibody
Sarilumab (Kevzara) SC	1	Used by adult patients who are intolerant to biological or non-biological disease-modifying antirheumatic drugs.[26]	Antibody
Pembrolizumab (MK-3475)	1	Treatment of recurrent or metastatic cervical cancer. Formula: $C_{6534}H_{10004}N_{1716}O_{2036}S_{46}$	Antibody
PD-1 blocking antibody + standard treatment	1	PD-1 acts as a negative regulator of T cell function. Monoclonal antibody blocking the activity of PD-1 can successfully reduce tumor load.[14]	Antibody
Azithromycin	16	Used for treatment of a number of bacterial infections. Formula: $C_{38}H_{72}N_2O_{12}$	Antibiotic
Carrimycin	1	This is effective against mycobacterium tuberculosis.[27]	Antibiotic
Ceftaroline	1	This is a cephalosporin antibiotic with anti-MRSA activity. Formula: $C_{22}H_{21}N_8O_8PS_4$	Antibiotic
Macrolide	1	Used to inhibit bacterial protein synthesis.	Antibiotic
Ceftriaxone	1	Used to treat severe or life-threatening bacterial infections. Formula: $C_{18}H_{18}N_8O_7S_3$	Antibiotic
Moxifloxacin	1	Used to treat bacterial infections of the lungs and stomach. Formula: $C_{21}H_{24}FN_3O_4$	Antibiotic
Levofloxacin	1	Used to treat bacterial infections, including pneumonia. Formula: $C_{18}H_{20}FN_3O_4$	Antibiotic
Amoxicillin-clavulanate	1	Used for treatment of a number of bacterial infections. Formula: $C_{24}H_{28}N_4O_{10}S$	Antibiotic
Atovaquone/azithromycin	1	Atovaquone is used to treat serious lung infection. Azithromycin is used to treat various bacterial infections.	Antibiotic
Piperacillin-tazobactam	1	The combination has activity against many Gram-positive and Gram-negative bacteria.	Antibiotic and inhibitor
Hydroxychloroquine sulfate + azithromycin	1	Hydroxychloroquine sulfate is an oral antimalarial medicine. Azithromycin is an antibiotic used for treatment of a number of bacterial infections.	Antimalarial and antibiotic
Vitamin C	6	Vitamin C acts as an antioxidant and helps to protect cells from damage caused by free radicals.	Dietary supplement
Vitamin D	3	Vitamin D allows the intestines to stimulate and absorb calcium and reclaim calcium.	Dietary supplement
Zinc	2	Zinc can significantly reduce risk of age-related infectious diseases and macular degeneration.	Dietary supplement
Glucose tablets	1	Used to treat hypoglycemia or low blood sugar.[14] Formula: $C_6H_{12}O_6$	Dietary supplement
Ascorbic acid	1	Used to treat low levels of vitamin C in people. Formula: $C_6H_8O_6$	Dietary supplement
Interferon beta-1a	2	Interferon beta-1a is used to treat multiple sclerosis. Formula: $C_{908}H_{1408}N_{246}O_{252}S_7$	Interferon
Interferon beta-1b	1	Used to treat relapsing/remitting multiple sclerosis. Formula: $C_{908}H_{1408}N_{246}O_{253}S_6$	Interferon
Recombinant human interferon α1β	2	Applied in the initial treatment and prevention of SARS and MERS.[14]	Interferon
Alpha-interferon nebulization	1	This mobilizes the body's immune system to fight cancer.	Interferon
Peginterferon lambda-1a	1	Pegylated type III interferon with marked anti-HCV activity which is mainly used for treatment of CHB.[28]	Interferon
Arbidol hydrochloride combined with interferon atomization	1	They are combined to treat SARS-CoV-2 viral pneumonia, so as to provide reliable evidence-based medicine for treating viral pneumonia.[14]	Antiviral and interferon
Huaier granules	1	Orally bioavailable traditional Chinese medicine (TCM) composed of granules containing an aqueous extract of *Trametes robiniophila* Murr (Huaier).	Traditional Chinese medicine
T89	1	T89 is a botanical drug for oral use. T89 can provide substantial benefits in the prevention or alleviation of symptoms associated with acute mountain sickness.	Traditional Chinese medicine
TCM	2	Traditional medicine includes various forms of herbal medicine, acupuncture, cupping therapy, gua sha, massage, bonesetter, exercise and dietary therapy.	Traditional Chinese medicine

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Table 3. Continuation

Drugs	Number of trials	Remarks	Drug category
Yinhu Qingwen granula	2	Yinhu Qingwen granula consists of 11 common nontoxic traditional Chinese medicines and previous vivo antiviral studies showed its activity for inhibition of COVID-19.[14]	Traditional Chinese medicine and antiviral
Xiyanping injection	1	Xiyanping is a TCM preparation with andrographolide as a principal component; it has significant antibacterial and antiviral effects.[29]	Traditional Chinese medicine and antiviral
YinHu QingWen decoction	2	This consists of 11 common nontoxic traditional Chinese medicines such as *Polygonum cuspidatum*, Honeysuckle, Nepeta, *Ligustrum lucidum*.[14]	Traditional Chinese medicine and antiviral
PUL-042 inhalation solution	2	This reduces the infection rate and progression to COVID-19 in adults exposed to SARS-COV-2.[14]	Inhaler
Ciclesonide metered dose inhaler	1	It is used to treat asthma and allergic rhinitis. Formula: $C_{32}H_{44}O_7$	Inhaler
Levamisole pill + budesonide + formoterol inhaler	1	Levamisole can increase lymphocytes.[14] Budesonide can suppress the immune reaction locally in the respiratory system.[14] Formoterol is a β2 agonist and can open airways.[14]	Inhaler
Sarilumab	6	Used for the treatment of rheumatoid arthritis. Formula: $C_{6388}H_{9918}N_{1718}O_{1998}S_{44}$	IL-6 receptor blocker
RoActemra IV	1	This is a first-in-class anti-IL-6 receptor (aIL-6R) therapy. IL-6 plays a key role in activating the inflammatory pathway.	IL-6 receptor blocker
Losartan	5	Losartan is an oral medication mainly used to treat high blood pressure. It may be used alone or in addition to other blood pressure medications.	Angiotensin receptor blockers
Valsartan	1	Valsartan is an oral medication used to treat high blood pressure, heart failure and diabetic kidney disease.[14] Formula: $C_{24}H_{29}N_5O_3$	Angiotensin II receptor blocker
Anakinra	3	Used to treat rheumatoid arthritis. Formula: $C_{759}H_{1186}N_{208}O_{232}S_{10}$	Receptor antagonist
Sargramostim	1	Sargramostim is a recombinant granulocyte macrophage colony-stimulating factor (GM CSF). Formula: $C_{639}H_{1006}N_{168}O_{196}S_8$	Biological response modifier
Methylprednisolone	5	Used to suppress the immune system. Formula: $C_{22}H_{30}O_5$	Corticosteroid
Dexamethasone	2	Used to reduce the duration of mechanical ventilation.[14] Formula: $C_{22}H_{29}FO_5$	Corticosteroid
Fingolimod	1	This is an effective immunological modulator. Formula: $C_{19}H_{33}NO_2$	Immunomodulator
Clopidogrel	1	Used to reduce the risk of heart disease. Formula: $C_{16}H_{16}ClNO_2S$	Inhibitor
Rivaroxaban	1	Used to treat and prevent blood clots. Formula: $C_{19}H_{18}ClN_3O_5S$	Inhibitor
Baricitinib	3	Used for the treatment of rheumatoid arthritis in adults. Formula: $C_{16}H_{17}N_7O_2S$	Inhibitor
Sildenafil citrate tablets	1	This is an oral therapy for erectile dysfunction. Formula: $C_{22}H_{30}N_6O_4S$	Inhibitor
Atorvastatin	1	Used to prevent cardiovascular disease. Formula: $C_{33}H_{35}FN_2O_5$	Inhibitor
Omeprazole	1	Used in treating gastroesophageal reflux disease. Formula: $C_{17}H_{19}N_3O_3S$	Inhibitor
Ruxolitinib	3	Used to treat myelofibrosis and polycythemia vera. Formula: $C_{17}H_{18}N_6$	Inhibitor
Cobicistat	1	Used to treat human immunodeficiency virus infection. Formula: $C_{40}H_{53}N_7O_5S_2$	Inhibitor
Camostat mesylate	2	Camostat mesylate can block entry of SARS-CoV-2 into cells. Formula: $C_{20}H_{22}N_4O_5$	Inhibitor
Tofacitinib	1	Tofacitinib can mitigate alveolar inflammation.[14] Formula: $C_{16}H_{20}N_6O$	Inhibitor
ARB/ACEI	1	Used to treat high blood pressure.	Inhibitor

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Table 3. Continuation

Drugs	Number of trials	Remarks	Drug category
Angiotensin 1-7	1	Angiotensin 1-7 is a vasodilator agent. Formula: $C_{41}H_{62}N_{12}O_{11}$	Inhibitor
RhACE2 APN01	1	This is believed to have the potential to inhibit COVID-19 infection and reduce lung injury.	Inhibitor
Nintedanib 150 mg	1	Used for treatment of idiopathic pulmonary fibrosis. Formula: $C_{31}H_{33}N_5O_4$	Inhibitor
Calcium channel blockers	1	Used to relax blood vessels and increase the supply of blood and oxygen to the heart.	Antihypertensive
Tranexamic acid	2	Used to treat excessive blood loss from major trauma. Formula: $C_8H_{15}NO_2$	Antifibrinolytic
Plasma	2	This helps to distribute heat throughout the body.	Plasma
Hyperimmune plasma	1	This can induce high serum concentrations of antibodies against Gram-negative LPS.[30]	Plasma
Tocilizumab	13	Used for treatment of rheumatoid arthritis. Formula: $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$	Other treatment/drug
BLD-2660	1	Used to reduce viral replication.[14]	Antifibrotic
Telemedicine	1	This allows healthcare professionals to evaluate, diagnose and treat patients using telecommunications technology.	Other treatment/drug
Oxyhydrogen	1	This is an adjuvant therapy for patients infected with COVID-19 pneumonia, for improving the clinical symptoms.[14]	Other treatment/drug
Best supportive care (BSC) + IFX-1	1	This is a phase II study with two treatment arms. It is used in patients with severe COVID-19 pneumonia.[14]	Other treatment/drug
Usual practice + Symbicort Rapihaler	1	Interventional patient will be treated with Symbicort Rapihaler, which is inhaled into the lungs to treat asthma.[14]	Other treatment/drug
Thymosin + standard treatment	1	Thymosin is used to regulate cellular immunity in sepsis patients.[14]	Other treatment/drug
Oxygen treatment	1	Oxygen treatment delivers oxygen gas for breathing.	Other treatment/drug
Physiological saline solution	1	A sterile solution of sodium chloride that is isotonic to body fluids; used to maintain living tissue temporarily.	Other treatment/drug
Aviptadil via intravenous infusion + maximal intensive care	1	Aviptadil is an analog of vasoactive intestinal polypeptide for treating erectile dysfunction. Maximal intensive care has been used for COVID-19-induced acute respiratory distress syndrome.[14]	Other treatment/drug
Normal saline infusion + Maximal intensive care	1	Maximal intensive care is defined not to include extracorporeal mechanical oxygenation.[14] This combination has been tested in relation to coronavirus infection.[14]	Other treatment/drug
Discontinuation and continuation of RAS blocker therapy	1	It is crucial to determine whether RAS blockers should be discontinued or not in patients with COVID-19.[14]	Other treatment/drug
Thiazide or thiazide-like diuretics	1	These are widely used for management of hypertension.	Other treatment/drug
Angiotensin receptor blocker	1	Angiotensin receptor blockers are medications that block the action of angiotensin II and allow arteries and veins to widen.	Other treatment/drug
Thymosin alpha 1	1	This is a peptide fragment derived from prothymosin alpha, a protein that in humans is encoded by the PTMA gene.	Other treatment/drug
Bromhexine 8 mg	1	Used to treat chest congestion and coughing. Formula: $C_{14}H_{20}Br_2N_2$	Other treatment/drug
Anluohuaxian	1	Used to block the progression of pulmonary fibrosis and improve lung function in patients with COVID-19.[14]	Other treatment/drug
Eicosapentaenoic acid gastro-resistant capsules	1	This is a hydrolytic breakdown product of eicosapentaenoyl ethanolamide. Formula: $C_{20}H_{30}O_2$	Other treatment/drug
Tradipitant	1	Used to treat motion sickness and atopic dermatitis. Formula: $C_{28}H_{16}ClF_6N_5O$	Other treatment/drug
RoActemra SC	1	This is an anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass.	Other treatment/drug
Defibrotide injection	1	This works by preventing formation of blood clots.	Other treatment/drug
Sterile water for injection	1	This preparation is designed solely for parenteral use, after addition of drugs that require dilution.	Other treatment/drug

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Table 3. Continuation

Drugs	Number of trials	Remarks	Drug category
Standard treatment/ medical care/ therapy	21	Standard therapy is the medical treatment that is normally provided to people with a given condition.	Other treatment/drug
Intravenous immunoglobulin	1	Intravenous immunoglobulin (IVIG) therapy can improve the prognosis for critically ill patients with SARS-CoV-2.[14]	Other treatment/drug
Oxygen therapy	1	Oxygen therapy is a treatment that provides supplemental oxygen.	Other treatment/drug
Deferoxamine	2	Used to treat transfusion-related chronic iron overload. Formula: $C_{25}H_{48}N_6O_8$	Iron chelator

ACE = angiotensin-converting enzyme; MMP = matrix metallopeptidases; PEP = post-exposure prophylaxis; RSV = respiratory syncytial virus; RNA = ribonucleic acid; VEGF = vascular endothelial growth factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; PD-L1 = programmed death-ligand 1; PD-1 = programmed cell death protein 1; MRSA = methicillin-resistant *Staphylococcus aureus;* HCV = hepatitis C virus; CHB = complete heart block; IL-6 = interleukin 6; RA = rheumatoid arthritis; ARDS = acute respiratory distress syndrome; CYP3A = cytochrome P450 3A; JAK1/3 = Janus kinase 1/3; ARB = angiotensin receptor blocker; ACEI = angiotensin-converting enzyme inhibitors; RAS = renin-angiotensin system; LPS = lipopolysaccharides; PTMA = prothymosin alpha; SC = subcutaneously; IV = intravenously; CC50 = cytotoxic concentration 50%.

Among these trials, 57 investigated antivirals, 57 antimalarials, 87 anti-inflammatories, 6 antiretrovirals, 13 dietary supplements, 21 standard treatment care, 9 traditional Chinese medicine, 6 oxygen and nitric acid therapy, 3 plasma, 11 antibodies, 26 antibiotics and several other therapeutics. Among these, some drugs, especially antiviral and antimalarial drugs, have shown effective results in ongoing treatment processes for COVID-19, and several patients have been successfully cured.[15] On the other hand, in some cases, these drugs have also shown negative results.[16] Thus, without proper results from successful clinical trials, specific therapeutics cannot be identified. However, most of these trials are expected to finish by the end of 2020, whereupon successful results from these trials will be able to assist in developing specific therapeutics for COVID-19 infection.

Vaccine and biological trials

With the rise of SARS-CoV-2, around 30 potential ongoing trials on vaccines have been classified in the registers of ClinicalTrials.gov (**Table 4**). A variety of technologies, including use of deoxyribonucleic acid (DNA)-based techniques, messenger ribonucleic acid (RNA)-based techniques, synthetic particles, nanoparticles and modified virus-like particles have been used. It will most probably take around a year for phase 1 clinical trials to begin in relation to a large proportion of the candidate vaccines, unless funded by the Coalition for Epidemic Preparedness Innovations (CEPI). However, a kit that was developed by Beijing Genomics Institute (BGI) passed the emergency approval process of the National Medical Products Administration of China and so it is currently being used in clinical and surveillance centers in China.[17] All of these trials are testing the immunogenicity and safety of their corresponding vaccine candidates relating to MERS-CoV, but have been excluded because of the unavailability of results so far. These trials are projected to be finished by December 2020 (two studies in Russia) and by December 2021 (in Germany).[18-19]

At present, vaccines for SARS-CoV-2 are still at the development stage and none are at the testing stage. On January 23, 2020, an announcement was made by the Coalition for Epidemic Preparedness Innovations (CEPI) that vaccine development programs will be funded by them in partnership with Moderna, University of Queensland and Inovio, with the aim of clinically testing the experimental vaccines within 16 weeks. The vaccine candidates will be developed using the DNA, recombinant and mRNA vaccine platforms of these organizations.[20]

Among the trials identified, vaccines based on the following are expected to show high potential as effective vaccines against COVID-19: natural killer (NK) cell group; mesenchymal stromal cell (MSC) group; bacille Calmette-Guérin (BCG); LV-SMENP-DC; CAStem; chimpanzee adenovirus Oxford 1 (ChAdOx1); aAPC; mRNA-1273; bacTRL-Spike; etc. However, convalescent plasma, high-titer anti-SARS-CoV-2 plasma, SARS-CoV-2 non-immune plasma and high-titer anti-SARS-CoV-2 plasma are bio-pharmaceutical products that have also been identified in clinical trial as vaccine candidates and are expected to have high potentiality to act against COVID-19. It would then be possible to successfully apply these vaccines if positive results are obtained from these registered trials.

Devices and products

To facilitate the treatment process relating to COVID-19 infection, several trials to develop device and products have been registered. In total, 31 trials relating to devices and products for COVID-19 had been registered up to April 12, 2020, which is more than the numbers of diagnostic test trials and vaccine trials. Most of

Table 4. Biologics and vaccines for use against COVID-19 identified in registered clinical trials

Biologics/vaccines	Number of trials	Remarks
NK cells	2	NK cells are essential for innate immunity and adaptive immunity.[14]
IL-15-NK cells	1	These show improved pharmacokinetic characteristics.[14]
NKG2D CAR-NK cells	1	NK cells modified by CAR have been demonstrated to be very safe without severe adverse events such as cytokine-releasing syndromes.[14]
ACE2 CAR-NK cells	1	These inhibit SARS-CoV-2 infection in type II alveolar epithelial cells.[14]
NKG2D-ACE2 CAR-NK cells	1	NKG2D-ACE2 CAR-NK cells are derived from cord blood and are used for providing safe and effective cell therapy for COVID-19.[14]
NestCell	1	NestCell is a mesenchymal stem cell therapy produced by Cellavita.[14]
WJ-MSCs	1	WJ-MSCs have been derived from cord tissue of newborns; screened for HIV1/2, HBV, HCV and CMV; and cultured to enrich for MSCs.[14]
MSCs	2	MSCs can significantly reduce pathological changes in lungs.[14]
Saline containing 1% human serum albumin (solution of MSC)	1	Human serum albumin is the serum albumin found in human blood and it is the most abundant protein in human blood plasma. Saline containing 1% human serum albumin has been tested for use against severe COVID-19.[14]
Pathogen-specific aAPC	1	aAPCs modified with lentiviral vector expresses synthetic minigenes based on domains of selected viral proteins.[31]
LV-SMENP-DC vaccine	1	LV-SMENP-DC vaccine is made by modifying DC with lentivirus vectors expressing COVID-19 minigene SMENP and immune modulatory genes.[14]
Antigen-specific CTLs	1	Used to produce autologous cell products for adoptive cell therapy.
Recombinant novel coronavirus vaccine (adenovirus type 5 vector)	1	This is currently being investigated for prophylaxis against SARS-CoV-2.
Dental pulp mesenchymal stem cells	1	These are tissue-specific adult stem cells and can undergo directed differentiation to multiple cell lineages including odontoblasts, osteoblasts, chondrocytes and adipocytes.
BCG vaccine	2	BCG vaccine is a vaccine primarily used against tuberculosis. It has broad power to boost the immune system against the novel coronavirus.
CAStem	1	CAStem is an injectable product composed of immunity and matrix-regulatory cells (IMRCs).[14]
Emapalumab	1	This is an anti-interferon-gamma antibody used for treatment of hemophagocytic lymphohistiocytosis, which currently has no cure.
Anakinra	1	Anakinra is a biopharmaceutical drug used as a second-line treatment to manage symptoms of rheumatoid arthritis after treatment with a disease-modifying antirheumatic drug (DMARD) has failed.
Human amniotic fluid	1	This is used for administration of amniotic fluid in SARS-CoV-2-positive patients.[14]
ChAdOx1 nCoV-19	1	ChAdOx1 nCoV-19 is a vaccine currently being investigated for prophylaxis against SARS-CoV-2.
Anti- SARS-CoV-2 plasma	1	This is collected through pheresis from volunteers who have recovered from COVID-19 disease.[14]
SARS-CoV-2 nonimmune plasma	1	This is the standard plasma collected prior to December 2019 to evaluate the efficacy of treatment among adults exposed to COVID-19.[14]
UC-MSCs	3	UC-MSCs are a class of cells with significant self-renewal and multi-lineage differentiation properties.[14]
Allogeneic human dental pulp stem cells (BSH BTC and Utooth BTC)	1	Used for routine treatment and intravenous injection.[14] The safety and efficacy of these cells have been evaluated in relation to treatment of severe pneumonia caused by COVID-19.[14]
Umbilical cord Wharton's jelly derived human MSCs	1	If all MSCs share several characteristics regardless of the tissue source, the highest productions of bioactive molecules and the strongest immunomodulatory properties are yielded by those from Wharton's jelly of the umbilical cord.[14]
Blood sampling	1	This is used to determine ACE2 levels and activity in patients with SARS-CoV-2 infection who are admitted to an intensive care unit.[14]
High-titer anti-SARS-CoV-2 plasma	1	This is an option for COVID-19 treatment and may be available from people who have recovered and can donate plasma.[14]
mRNA-1273	1	mRNA-1273 is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine.[14]
SARS-CoV-2 PCR	1	This is used to evaluate the virological and clinical outcomes among subjects exposed to contacts presenting high or moderate risk of SARS-CoV-2 transmission.[14]
bacTRL-spike	1	This has been engineered to deliver plasmids containing synthetic DNA-encoding spike proteins from SARS-CoV-2.[14]
MSC-derived exosomes	1	These enable significantly reduced lung inflammation and pathological impairment resulting from different types of lung injury.[14]
Anti-SARS-CoV-2 convalescent plasma	2	This is an option for treatment of COVID-19 and may be rapidly available when there are sufficient numbers of people who have recovered and can donate high-titer neutralizing immunoglobulin-containing plasma.[14]

NK = natural killer; IL-15 = interleukin-15; ACE2 = angiotensin-converting enzyme 2; WJ-MSCs = mesenchymal stem cells from Wharton's jelly; MSCs = mesenchymal stem cells; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; CMV = cytomegalovirus; CTLs = cytotoxic T lymphocytes; BCG = bacille Calmette-Guérin; ChAdOx1 = chimpanzee adenovirus Oxford 1; UC-MSCs = umbilical cord-derived mesenchymal stem cells; mRNA = messenger ribonucleic acid.

the devices in these trials related to oxygen supply and monitoring, sensors, image processing, high-flow nasal cannulas, inspiratory and expiratory training devices, MAGEC spine rods (NuVasive, California, United States), echocardiography devices, transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) and apps for COVID-19 patients. All these devices are expected to be highly effective for treating COVID-19 patients. Therefore, before applying these devices rapidly, the medical world needs to wait until positive finished results are received, in order to avoid any kind of negative effects on patients (**Table 5**).

Table 5. Devices and products for use against COVID-19 identified in registered clinical trials

Devices/products	Number of trials	Remarks
Web application	1	Used to assess the evolution of the number of calls to the emergency service within 12 days after the launch of the application.[14]
Hyperbaric oxygen therapy (HBOT) device	1	This delivers pure oxygen in a pressurized room or tube.[14]
GO2 PEEP mouthpiece	2	This effectively delivers PEEP with every breath of patients.[14]
Oxyhydrogen device	1	Used to improve symptoms of patients with COVID-19.[14]
Oxygen monitoring device	1	Used for monitoring peripheral blood oxygen saturation and oxygen concentration.[14]
CT-V	1	Used to detect parenchymal lung function changes at a voxel level.[14]
vv-ECMO + cytokine adsorption (CytoSorb adsorber)	1	This combination can lead to reduction of the levels of circulating pro and anti-inflammatory cytokines.[14]
vv-ECMO only (no cytokine adsorption)	1	This provides support for the lungs. It is used in situations of acute respiratory failure in COVID-19-disease.[14]
VivaDiag* COVID-19 IgM/IgG	1	This is used to evaluate the immune response of negative patients during the outbreak of COVID-19.[14]
A mindfulness meditation mobile app - Calm v4.22	1	This app includes meditation lessons, sleep stories (bedtime stories for grown-ups), sleep music and nature sounds.[14]
Medical/surgical mask	2	This is a loose-fitting disposable device for creating a physical barrier.
N95 respirator	1	This is a respiratory protective device.
High-flow nasal cannula (HFNC)	1	This is a device that can deliver 100% humidified and heated oxygen.
Inspiratory training device	1	This is a device that is used to determine the effectiveness and safety of respiratory training in relation to preventing and reducing the severity of COVID-19.[14]
Expiratory training	1	This tends to improve coughing and reduce the sensation of respiratory effort.[32]
Cordio app v1.54	1	This app uploads vocal data to the sponsor's servers for analysis.[14]
Biosensors	1	These detect changes in respiration, temperature and circulation.[14]
SensiumVitals** wearable sensor	1	This sensor measures heart rate, respiratory rate, temperature and suspected coronavirus in a designated location (e.g. a hotel).[14]
CVVH machine	1	This has the aim of clearing CO_2 and improve oxygenation.[14]
MAGEC spine rod***	1	Magnetically controlled spine rod for treatment of scoliosis.[14]
Transpulmonary thermodilution	1	Transpulmonary thermodilution is a technique that provides a full hemodynamic assessment.[33]
Echocardiography	1	Echocardiography is a test that uses sound waves to produce live images of the heart.
TAVR or SAVR	1	Used to describe rates of morbidity and mortality.[14]
CPAP treatment device	1	CPAP is a common treatment for obstructive sleep apnea.
Home blood pressure monitoring device - Qardio Arm (Qardio, California, United States)	1	Home blood pressure device with telemonitoring capability that allow participants and their physicians to monitor blood pressure over time and to titrate blood pressure medications as needed for persistently elevated blood pressure.[14]
Automated oxygen administration - FreeO2 device (OxyNov Inc, Quebec, Canada)	1	This provides a solution for reducing the number of interventions by healthcare workers relating to oxygen therapy, so as to reduce complications relating to oxygen and improve monitoring.[14]
CELLECTRAÂ**** 2000	1	This is applied to increase the permeability of cell membranes to enhance the uptake of drugs or vaccines into target cells.[34]
Caption AI	1	Software program to take the best possible pictures of the heart.[14]
Stem Cell Educator-Treated Mononuclear Cell Apheresis (Tianhe Stem Cell Biotechnologies Inc, Shandong, China)	1	This circulates a patient's blood through a blood cell separator, briefly cocultures the patient's immune cells with adherent CB-SC in vitro, and returns the "educated" autologous immune cells to the patient's circulation.[14]
COVID-19 Symptom Tracker app v0.3	1	This records and monitors the symptoms of COVID-19 coronavirus infection; tracking in real time how the disease progresses.[14]

PEEP = positive end-expiratory pressure; CT = computed tomography; vv-ECMO = veno-venous extracorporeal membrane oxygenation; IgM = immunoglobulin M; IgG = immunoglobulin G; COPD = chronic obstructive pulmonary disease; CVVH = continuous veno-venous hemofiltration; NCP = novel coronavirus pneumonia; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement; AI = artificial intelligence; CB-SC = cord blood stem cells.
*Everest Links Pte Ltd, Midview City, Singapore; **Sensium Healthcare Ltd, Oxford, United Kingdom; ***NuVasive, California, United States; ****Inovio Pharmaceuticals, Pennsylvania, United States.

Behavioral and other clinical trials

In order to facilitate the treatment process for COVID-19 infection, 65 behavioral and other trials were registered up to April 12, 2020. Most of these behavioral and other trials relate to guidelines, management, healthcare, surveys on anxiety, mood and quality of life and human biological samples, which are very necessary in relation to COVID-19 patients. Standard public health measures have been used to isolate patients and do contact tracing as per national guidelines.[14] Video-based aerobic exercises have been used to increase physical activity levels, psychological condition and physical wellbeing.[14] Blood sampling is necessary in order to detect COVID-19 seroconversion among medical and paramedical staff. Retrospective analysis is used in order to clearly understand the impact factors of clinical outcomes among hospitalized patients.[14] Pulmonary ultrasound is used to assess the risk of severe clinical outcomes in patients with suspected or diagnosed COVID-19.[14] The SPIN-CHAT software is used to evaluate videoconference-based interventions that are designed to improve the symptoms of anxiety and other mental health outcomes.[14] Moreover, all the trials are expected to be highly effective if the results are positive with regard to treating COVID-19 patients. Additionally, before applying the results in practice, further experiments and studies should be done, to avoid any harmful effects or adverse events in relation to patients.

DISCUSSION

This study was based on the database of ClinicalTrials.gov up to April 12, 2020. Most of the trials are being conducted in the United States and China. Since COVID-19 has spread all over the world, there is a growing need to also conduct investigations in other countries that have been affected. Moreover, most of the trials are in phase 2 and some trials have longer expected completion times.

SARS-CoV-2 is a very dangerous virus that is rapidly spreading all over the world. For effective solutions to be obtained quickly, trials should be completed within a short time. However, regulatory authorities need to carefully maintain proper recruitment protocols for clinical trials.

Observational studies account for slightly more than one-fourth of the total number of studies. This proportion needs to be increased somewhat, because observational studies directly focus on treatment protocols for COVID-19 patients. More studies should be conducted with numbers of participants above 1000, in order to find more accurate results. Since every person is important for proper investigation, more people with ages below 18 should be included.

The largest proportion of the trials relates to drugs. However, there need to be greater numbers of trials relating to other categories. Although antiviral drugs (remdesivir and lopinavir/ritonavir) and antimalarial drugs (especially hydroxychloroquine), plasma therapy, anti-inflammatory drugs and azithromycin have been investigated in the highest proportion of the trials, no accurate results that can be completed early have yet been found with regard to combating COVID-19. Moreover, some of the drugs investigated may have serious adverse events. Therefore, adequate precautions should be taken before applying a drug, to avoid any negative impacts. Successful conclusions from these trials are important and the results are expected to be received mostly at the end of 2020.

Since COVID-19 has a very high transmission rate, diagnostic tests are very important. Through these tests, people with the virus can be isolated. Otherwise, the virus may spread very quickly.

Polymerase chain reaction (PCR) tests, immunoglobulin G antibody testing kits and serological tests have been registered for trials in high numbers. However, more clinical trials are still needed in order to identify more efficient testing processes that have low cost and high detection rates within a short time, to control the transmission rate. Vaccines can be very effective to protect people from COVID-19, so more importance should be given to finding at least one effective vaccine as soon as possible. Overall, use of convalescent plasma, high-titer anti-SARS-CoV-2 plasma and SARS-CoV-2 non-immune plasma may show potential in relation to vaccines for treating COVID-19.

Moreover, to facilitate the treatment process, more effective devices, especially for oxygen therapy and patient monitoring systems, are important. Additionally, behavioral and other trials are also needed in order to understand and analyze healthcare management for COVID-19 and its impact on society, patients and medical science.

The world is now counting the days, in the hope of receiving positive successful results from the ongoing clinical trials as soon as possible, to combat COVID-19.

CONCLUSIONS

This review found 339 clinical trials that evaluated interventions for preventing or treating coronavirus. Overall, use of antiviral drugs (remdesivir and lopinavir/ritonavir) and antimalarial drugs (especially hydroxychloroquine), plasma therapy, anti-inflammatory drugs and azithromycin may present some benefits for treating COVID-19 infection. Polymerase chain reaction (PCR) tests, immunoglobulin G antibody testing kits and serological tests are the diagnostic tests that are involved in the highest numbers of trials registered for detecting COVID-19. Moreover, several kinds of plasma and bio-pharmaceutical products identified in trials may present potential as candidate vaccines against COVID-19. Additionally, trials on devices (oxyhydrogen devices, patient monitoring devices, etc.) and other clinical trials (surveys, behavioral trials and observational trials) may also have potential to facilitate the treatment process for COVID-19. However, completion results from the trials described in the present study are needed before any diagnostic

test, therapeutics, vaccines, devices or other objects relating to clinical management processes for COVID-19 can be properly recommended. More randomized controlled trials are still necessary, in order to reduce the uncertainties regarding most clinical questions that surround COVID-19.

LIMITATIONS

This study had some limitations. It was conducted within time limits and details of some trials were not properly available.

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Address for correspondence:
Farzad Hossain
Department of Mechanical and Production Engineering, Islamic University of Technology, Gazipur-1704, Bangladesh
Tel. (+880) 1840199782
E-mail: farzadhossain@iut-dhaka.edu

Knowledge, attitudes and practice among physicians during the COVID-19 pandemic

Viroj Wiwanitkit[I]

Dr DY Patil University, Pune, India

[I]MD. Honorary professor, Dr DY Patil University, Pune, India.
orcid.org/0000-0003-1039-3728

Dear Editor,

I would like to share some ideas on the article "Evaluation of knowledge and attitudes among intensive care physicians during the COVID-19 pandemic: a cross-sectional survey", which was published in the Sao Paulo Medical Journal.[1] Erbas et al. concluded that "*For intensive care treatment of COVID-19 patients, many factors require management, and clinicians' experience is guiding future processes*".[1]

Since COVID-19 is a new emerging disease, the data available for effective diagnostic and therapeutic management are limited. When a disease first occurs in a country, there is no doubt that practitioners usually only have limited knowledge. For example, in Thailand, the second country in which COVID-19 occurred,[2] the knowledge of local practitioners was not good when the disease first occurred.[3]

Therefore, the key important thing is medical education for practitioners. During a crisis, the data available changes rapidly and there is usually a problem in communication. Information technology (IT) may play a role, but its availability remains limited in remote areas. Additionally, because of the high influx of patients, practitioners might not have any time for education. A good plan for medical education for practitioners who have to care for these patients is necessary.

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Address for correspondence:
Viroj Wiwanitkit
Department of Community Medicine, Dr DY Patil University, Pune, India 411018
Tel. +91 020 27805217
E-mail: wviroj@yahoo.com

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The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

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All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. Each author should indicate a valid, up-to-date email address for contact;
7. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
8. Place or institution where the work was developed, city and country.
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh. These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the "doi" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of

sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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