การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมานอาการแสดงทางคลินิกของโรค การตรวจวินิจฉัย การดูแลรักษาและผลลัพธ์ของโรคติดเชื้อไวรัสโคโรนา 2019 ในแผนกฉุกเฉิน

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บทคัดย่อ

◗ บทนำ

แผนกฉุกเฉินถือเป็นสถานที่ด่านหน้าในการดูแลรักษาผู้ป่วยที่มารับบริการและสงสัยมีโรคติดเชื้อไวรัสโคโรนาสายพันธุ์ 2019 (โรคโควิด 19)

◗ วัตถุประสงค์

เพื่อทบทวนข้อมูลอาการแสดงทางคลินิกของโรค การตรวจวินิจฉัย การดูแลรักษาและผลลัพธ์ของผู้ป่วยสงสัยเป็นโรคโควิด 19 ที่มารับการรักษาในแผนกฉุกเฉิน

◗ วิธีดำเนินการวิจัย

ผู้วิจัยสืบค้นบทความจากฐานข้อมูล PubMed, Scopus และ Cochrane Library เพื่อหางานวิจัยประเภทการศึกษาตามรุ่น รายงานกรณีศึกษาผู้ป่วยแบบเดี่ยวและผู้ป่วยแบบกลุ่มที่มีข้อมูลด้านอาการแสดงทางคลินิกของโรค การตรวจวินิจฉัยและการดูแลรักษาผู้ป่วยในแผนกฉุกเฉิน จากนั้นผู้วิจัยนำข้อมูลที่ได้จากการศึกษาเหล่านี้มาทำการทบทวนวรรณกรรมอย่างเป็นระบบและวิเคราะห์อภิมานข้อมูลจากการศึกษาตามรุ่น

🔻 ผลการวิจัย

    ผู้วิจัยสามารถรวบรวมข้อมูลจากการศึกษาตามรุ่นได้ 12 ฉบับ และจากรายงานกรณีศึกษาผู้ป่วย แบบเดี่ยวและผู้ป่วยแบบกลุ่มได้ 40 และ 14 ฉบับตามลำดับ ผลการศึกษาตามรุ่นพบว่าผู้ป่วยโรคติดเชื้อ ไวรัสโคโรนา 2019 มักมีประวัติสัมผัสกับผู้ป่วยโรคเดียวกัน (46%, 95% CI 42-49)หรือมีประวัติเดินทาง ไม่นานก่อนมีอาการ (24%, 95% CI 11-37) อาการนำที่พบบ่อยสุดได้แก่ ไอ (79%, 95% CI 71-86%), มีไข้ (61%, 95% CI 40-81%) และหายใจลำบาก (48%, 95% CI 36-61) ส่วนอาการจมูกไม่ได้กลิ่น และลิ้นไม่รับรสนั้นมักพบได้น้อยในแผนกฉุกเฉินแต่ผู้ป่วยที่มีอาการเหล่านี้มีโอกาสตรวจพบโรคโควิด 19 สูงมาก (ความเสี่ยงสัมพัทธ์ 6.20; 95% CI 1.82-21.14) โรคติดเชื้อไวรัสนี้ทำให้ผู้ป่วยมาแผนกฉุกเฉินด้วย ภาวะหลอดเลือดสมองตีบเฉียบพลันหรือผื่นผิวหนังอักเสบได้ด้วยแต่ยังพบได้น้อย อาการทางระบบทาง เดินอาหารพบได้ร้อยละ 10-20 ข้อมูลสัญญาณชีพแรกรับนั้นไม่แตกต่างกันระหว่างผู้ป่วยกลุ่มที่ติดเชื้อ ไวรัสโคโรนา 2019 และกลุ่มไม่ติดเชื้อ อย่างไรก็ตามผู้ป่วยกลุ่มที่ติดเชื้อไวรัสพบว่ามีอัตราการถูกใส่ท่อช่วย หายใจมากกว่ากลุ่มที่ไม่ติดเชื้อถึงสามเท่า (ความเสี่ยงสัมพัทธ์ 3.59; 95% CI 1.48-8.69) และมีผลตรวจ ทางห้อง ปฏิบัติการที่มักพบภาวะเม็ดเลือดขาดชนิดลิมโฟไซต์ต่ำ (71%, 95% CI 64-78) และจากเอกซเรย์ ปอดพบมีฝ้าขาวในปอดทั้งสองข้าง (60%, 95% CI 57-63)

🔻 สรุป

    ผู้ป่วยโรคติดเชื้อไวรัสโคโรนา 2019 ที่มารับการตรวจในแผนกฉุกเฉินจะมีอาการและอาการแสดง ทางคลินิกที่หลากหลาย นอกจากอาการทางระบบหายใจแล้วยังพบอาการจากระบบทางเดินอาหาร ระบบ ประสาทและผิวหนังที่ผิดปกติได้ด้วย ผู้ป่วยกลุ่มนี้มีแนวโน้มถูกใส่ท่อช่วยหายใจมากขึ้น ดังนั้นแพทย์ เวชศาสตร์ฉุกเฉินควรเตรียมพร้อมสำหรับการใส่ท่อช่วยหายใจที่มีประสิทธิภาพและปลอดภัยต่อผู้ป่วยและ ผู้ที่ทำหัตถการ

🔻 คำสำคัญ

    โรคโควิด 19, ไวรัสโคโรนา, ไวรัสซาร์ส-โควี-2, อาการแสดงทางคลินิก, แผนกฉุกเฉิน, Clinical manifestation, investigation, management and outcomes of patients with suspected or confirmed COVID-19 in emergency departments: a systematic review and meta-analysis
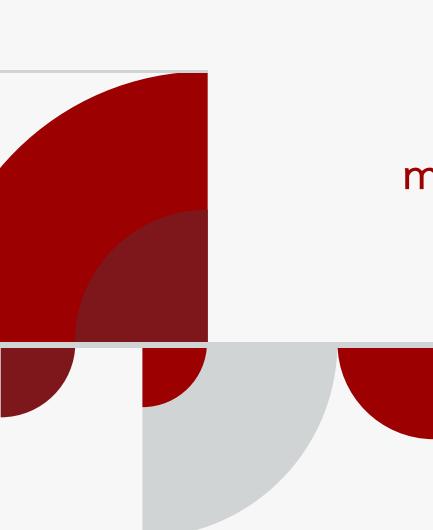
Clinical manifestation, investigation, management and outcomes of COVID-19 in emergency departments: a systematic review and meta-analysis

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Abstract

Introduction

Emergency departments are the frontline for managing patients suspected of having coronavirus disease 2019 (COVID-19).

Objective

To review the clinical manifestation, investigation, management and outcomes of patients with suspected COVID-19 in the emergency department (ED) setting.

Methods

We searched PubMed, Scopus and the Cochrane Library databases for case reports, case series and cohorts exploring the clinical manifestation, investigation and management of patients presenting to emergency department. We conducted a systematic review of the included studies and a meta-analysis of the cohorts.

Results

We included 40 case reports, 14 case series and 12 cohort studies in this sys-tematic review. Based on cohort studies, patients typically presented with a history of sick contact (46%, 95% CI 42-49) or recent travel (24%, 95% CI 11-37). Cough (79%, 95% CI 71-86%), fever (61%, 95% CI 40-81%) and shortness of breath (48%, 95% CI 36-61) were the most common chief complaints. Although rarely present in ED patients, de-creased taste and smell significantly increase the probability of testing positive for COVID-19 (risk ratio 6.20; 95% CI 1.82-21.14). Several rare clinical presentations of COVID-19 include stroke and skin rashes. Gastrointestinal symptoms could be found in up to 10-20% of patients. Although initial vital signs were not different between those who tested positive and negative for COVID-19, the intubation rate in the ED was triple in those with COVID-19 (risk ratio 3.59; 95% CI 1.48-8.69). Notable investigations were lymphopenia (71%, 95% CI 64-78) and bilateral infiltration on chest X-ray (60%, 95% CI 57-63).

Conclusion

Patients with COVID-19 could present to EDs with typical respiratory symptoms as well as several unusual manifestations, including gastrointestinal, neurological and dermatologi-cal problems. Since the intubation rate tripled in those with COVID-19 compared to those with-out. Thus, emergency physicians should prepare for effective intubation while keeping patients and providers safe

Keywords: COVID-19, Coronavirus, SARS-CoV-2, Clinical manifestation, Emergency department

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has led to the current global health crisis. As of August 2021, there have been over 212 million cases worldwide and over 4 million deaths.[1] The health systems of many countries have been overwhelmed by the in-creased demand for health care services.[2,3]

Emergency departments (EDs) are undoubtedly the frontline health facilities for the management of patients with severe COVID-19. As the sites of resuscitation of severe patients and unscheduled emergent visits and the safety nets for uninsured patients, EDs are compelled to treat all patients including patients with possible COVID-19.[4] A high index of suspicion and accurate clinical diagnosis are crucial for the early detection and management of this disease.

Despite a substantial increase in reviews on clinical presentations and treatment outcomes of COVID-19 in hospitalized patients, there have been few cohorts and systematic review regarding the clinical manifestation, management and outcomes of patients with COVID-19 in EDs since the beginning of the COVID-19 epoch.

Moreover, the signs and symptoms of COVID-19 are nonspecific and vary greatly in severity, ranging from asymptomatic infection to severe pneumonia with multiple organ failure and death. Sporadic case reports from worldwide resources potentially provide insights into the unique and rare presentation of COVID-19, which could help emergency physicians es-tablish suspicion in patients with rare manifestations of COVID-19.

Therefore, we conducted a systematic review and meta-analysis of the clinical mani-festations, investigations, management and outcomes in the emergency department to provide comprehensive pictures of these patients in the emergency department. We also aimed to compare the characteristics of emergency patients with confirmed COVID-19 and those without disease in search of unique trait for COVID-19 which emergency health providers could use as early tool for early diagnosis and effective isolation.

Methods

Search strategy

We searched PubMed, Scopus and the Cochrane Library databases for studies

from inception to May 21, 2020, using the search terms "COVID-19" and "emergency depart-ment". The reference lists of the review articles were reviewed. There was no language restriction. Articles written in languages other than English were translated into English using Google Translate.

Study selection

Since there were no clinical trials related to the topics of COVID-19 and emergency departments at the time of the search, The study inclusion criteria consist of case reports, case series, retrospective and prospective cohort studies that reported on either the clinical manifestation, investigation management or clinical outcomes in emergency department pa-tients with suspected or confirmed COVID-19. There was no restriction on follow-up duration or study size. The exclusion criteria are review articles opinions and study protocols.

Two authors (WT and JS) independent-ly screened the titles and abstracts of the searched records to identify potential studies. The full-text articles were retrieved and screened independently by the two authors to assess eligibility. Disagreements on study inclusion were resolved by consensus as suggested by another author (KM).

Studies were categorized into three groups based on their definitions. The selected case reports were studies that described individual patients regarding their clinical aspects. Case series were studies that serially described more than one patient without a control group and could not be reanalyzed to provide risk outcomes. Cohort studies serially included more than one patient with a control group.[5] The included cohorts were assessed for methodological quality using the Newcastle–Ottawa Scale (NOS) for cohort studies.[6] The case reports and case series were assessed for methodological quality using the proposed tools.[7,8]

Data extraction

The two authors independently extracted data from the included studies, including the following study characteristics: study name, country, month of publication and month of the study, study design, number of patients, emergency department census, and demographic data.

The following study outcomes were extracted: clinical manifestation, including history and physical signs, time at contact

and time of the first manifestation, labora-tory findings, imaging results management, disposition and clinical outcomes.

Statistical analysis

Data are reported as the percentages, means (SDs) or medians (interquartile ranges: IQRs), as appropriate. means (standard deviation: SD) or medians (interquartile ranges: IQRs) as appropriate.

Regarding case reports and case series, their results were synthesized qualitatively and quantitatively. The results of the cohort studies were synthesized quantitatively by conducting random-effects model meta-analyses in computing pooled risk ratios (RRs) for binary variables and weighted mean differences for continuous variables and reported with 95% CIs. Continuous outcomes were reported as means (SD), the (IQR) or range were estimat-ed as the means (SD) for the purpose of meta-analysis.[9] Heterogeneity among study effect sizes was assessed us-ing the I^2 index. An I^2 greater than 75% was regarded as considera-ble heterogeneity. The statistical significance level was defined as $p < 0.05$. All analyses were performed using STATA version 16 (College Station, TX, USA).

Results

Overall, 1499 articles were identified from the database search, which included 1238 from PubMed, 204 from Scopus and 7 from the Cochrane Library. We identified one additional record identified through other sources. After removal of duplicates, 1310 titles and abstracts were screened, and 277 full texts were retrieved and screened for eligibility. In total, 66 articles were included in this systematic review, consisting of 40 case reports, 14 case series and 12 cohort studies (Figure 1).

Systematic review and meta-analysis of cohort studies

Twelve cohort studies reported the outcomes of patients diagnosed with COVID-19.[10-21] In 7 out of 12 studies, the information of the patient under investigation (PUI), which subsequently tested negative for COVID-19, was also reported. The result of the reporting quality of the cohort is shown in table S1 (available in the supplementary file).

Meta-analysis of patients with COVID-19

The meta-analysis of patient characteristics, investigation, management
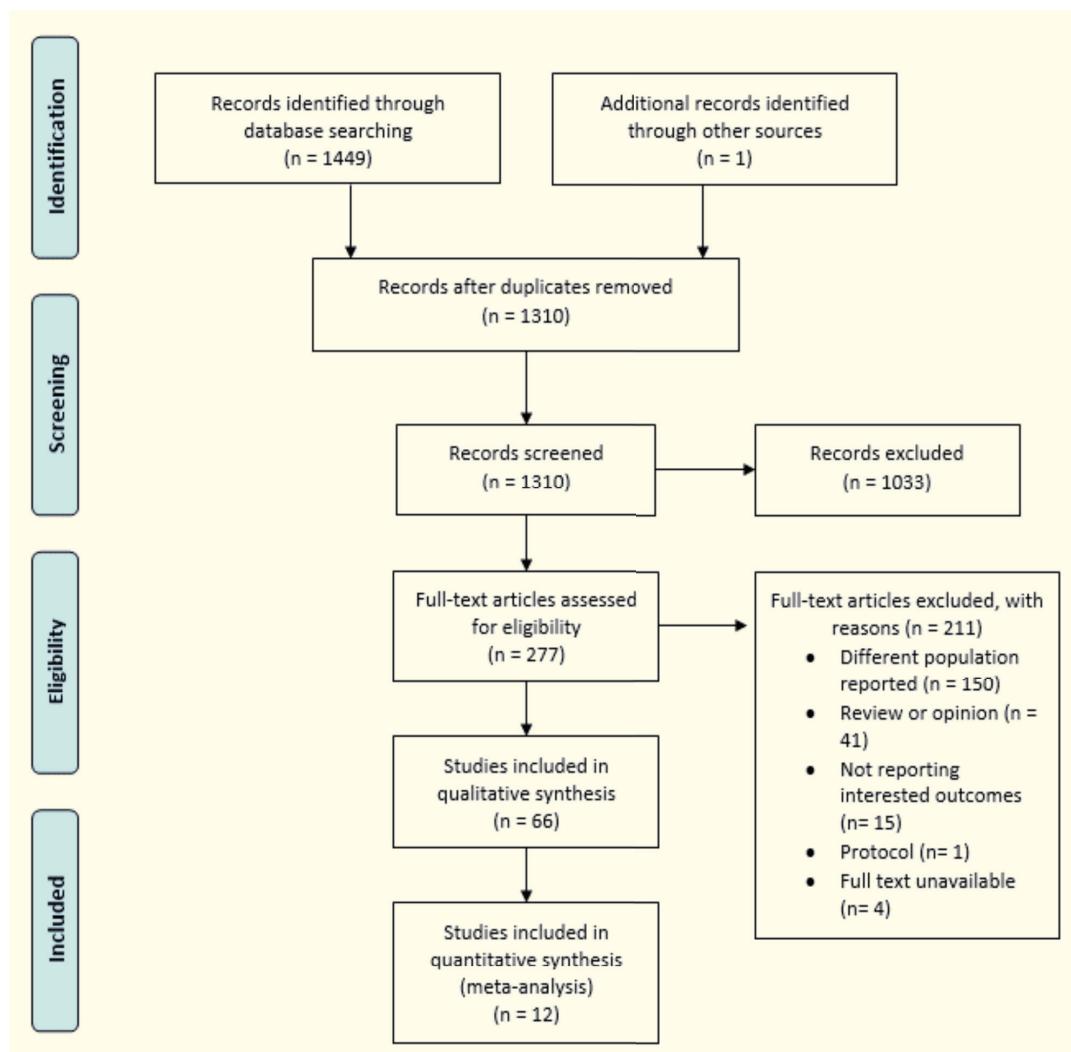
Figure 1 PRISMA diagram showing process of the literature search and trial selection

and outcomes of COVID-19-positive patients in the emergency department is shown in table 1. The aver-age age of the patients was 48 years old, with 44% being females. Patients mostly had comorbid cardiac diseases (24%, 95% CI 6-41%), hypertension (21%, 95% CI 14-29%) and diabetes mellitus (14%, 95% CI 11-16%). Almost half of the patients had a history of sick contact (46%, 95% CI 42-49%), and a quarter of the patients had a history of recent travel (24%, 95% CI 11-37%). They usually presented approximately 4 days after symptom onset, and the most

Table 1 Summary measures of data from cohort studies showing characteristics, investi-gation, management and outcomes of patients with COVID-19 in emergency departments.

Variables	Number of studies	Number of patients	Point estimates (95% CI)	I^2 (%)
Age (years old)	9	2406	47.95 (47.23 – 48.57)	98.7
Sex: Female (%)	11	2502	44% (37 – 51)	85.39
Ethnicity: White (%)	4	2118	42 (27 – 57)	96.42
Ethnicity: Asian (%)	4	2118	8 (3-13)	87.12
Ethnicity: African American (%)	4	2118	10 (2-18)	97.58
Ethnicity: Hispanic (%)	4	2118	29 (21-37)	85.97
Comorbidity (%)				
• Asthma	3	2089	10 (5-15)	86.06
• COPD	3	1783	3 (0-5)	66.96
• HT	5	2132	21 (14-29)	86.78
• Diabetes Mellitus	6	2239	14 (11-16)	40.65
• CKD	3	1783	5 (4-6)	0
• Malignancy	4	1794	4(3-5)	0
• Cardiac disease	5	1868	24 (6-41)	95.63
Health care provider (%)	2	1751	8 (7-10)	0
Current smoker (%)	2	314	21(12-29)	35.5
Exposure: sick contact (%)	6	1853	46 (42-49)	8.67
Exposure: travel (%)	5	203	24 (11-37)	79.27
Clinical manifestation				
Average day symptom to presentation ED (days)	4	488	4.64 (4.38 – 4.89)	93.7
Fever (%)	6	1928	61 (40-81)	97.57
Cough (%)	4	1792	79 (71-86)	68.12
Sore throat (%)	2	107	21 (14-29)	0
Rhinorrhea/congestion (%)	2	107	17 (10-24)	0
Decreased taste/smell (%)	3	137	10 (0 – 33)	81.56
Shortness of breath(%)	3	1761	48 (36-61)	79.54

Table 1   Summary measures of data from cohort studies showing characteristics, investi-gation, management and outcomes of patients with COVID-19 in emergency departments. (Ext.)

Variables	Number of studies	Number of patients	Point estimates (95% CI)	I^2 (%)
Fatigue (%)	3	1760	39 (14-66)	95.33
Diarrhea (%)	5	1900	22 (11-33)	93.9
Nausea/vomiting(%)	2	1751	13 (11-15)	0
Chest pain/chest discomfort (%)	3	239	19 (9-29)	74.14
Headache (%)	2	132	8 (4-13)	0
Physical Examination				
SpO2 (%)	3	1712	95.21 (94.95 – 95.47)	98
Heart rate (/min)	2	1683	94.45 (92.38 – 96.32)	96.6
Respiratory rate (/min)	2	1683	19.96 (19.69 – 20.23)	0
Body temperature (Degree Celsius)	3	1694	37.38 (37.32 – 37.43)	86.6
Systolic blood pressure (mmHg)	2	1662	143.04 (130.98 – 133.10)	23.3
Fever (%)	2	445	35 (31-39)	0
Investigation				
WBC (/uL)	4	957	7.17 (6.91 – 7.44)	94
Leukocytosis (%)	3	167	11 (6-16)	0
Neutrophil count (/1,000 uL)	2	126	4.38 (3.99 – 4.78)	84.5
Lymphocyte count (/1,000 uL)	2	126	1.12 (0.99 – 1.25)	0
Lymphocyte per-centage	2	829	15.91 (15.22 – 16.61)	95.3
Lymphopenia (%)	2	157	71 (64 – 78)	0
Platelet count (/1, 000 uL)	3	204	207.33 (195.44 – 219.23)	97.9
LDH (U/L)	3	854	366.34 (354.84 – 377.83)	97.5
CRP (mg/dl)	4	931	10.32 (9.72 – 10.91)	75.2%
Bacterial coinfection (%)	2	207	14 (10 – 19)	0

Table 1   Summary measures of data from cohort studies showing characteristics, investi-gation, management and outcomes of patients with COVID-19 in emergency departments. (Ext.)

Variables	Number of studies	Number of patients	Point estimates (95% CI)	I^2 (%)
Imaging (%)				
Total CXR	4	2100	67 (53 – 81)	86.88
CXR: no infiltration	4	1371	42 (26-59%)	95.19
CXR: Bilateral infiltration	2	954	60 (57 – 63)	0
Total CT chest	5	1806	44 (9-82)	98.22
CT chest: bilateral ground glass opacity	4	275	92 (79-100)	63.47
CT chest: crazy paving pattern	2	44	10 (2-21)	0
Management (%)				
Intubation in the ED	5	1990	9 (5-13) %	81.62
Disposition (%)				
Discharge	7	2186	40 (25 – 57)	96.74
Total admission	7	2286	41 (32-51)	90.01
Ward admission	4	1869	40 (24 – 56)	93.93
ICU admission	4	1869	4 (3-5)	0
Final outcome* (%)				
Mortality in ED	3	1769	0 (0-1)	42.79
In-hospital mortality	5	2202	5 (2-8)	90.56
Hospital LOS (days)	2	1751	1.46 (1.33 – 1.59)	98.9

BT: Body temperature; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: Computed tomography; CXR: Chest X-ray; ED: Emergency department; HR: Heart rate; HT: Hypertension; ICU: Intensive care unit; LDH: Lactate dehydrogenase; LOS: length of stay; RR: Respiratory rate; SBP: Systolic blood pres-sure; SpO2: Oxygen saturation; WBC: White blood cell count

*Data for the outcomes are not available for all patients, as some of them were still in hospi-tals at the time of publishing.

common complaints were cough (79%, 95% CI 71-86%), fever (61%, 95% CI 40-81%), shortness of breath (48%, 95% CI (36-61%) and fatigue (39%, 95% CI 14-66%). The average body temperature on presentation was 37.4 degrees Celsius, and patients presented with fever in only 35%. The average vital signs were generally stable, with an average heart rate of 94/min, systolic blood pressure of 143 mmHg respiratory rate of 20/min, and SpO2% of 95%. The complete blood count frequently revealed lymphopenia (71%, 95% CI 64–78)) but rarely leukocytosis (11%, 95% CI 6-16)). Chest X-rays were ordered in 67% (95% CI 53–81) of patients but were normal in 42%of the orders. CT chests were ordered in 44% (9-82) of patients, which revealed bilateral ground glass infiltration in 92% (95% CI 79-100%) of the orders. Of all patients, (9%, 95% CI 5-13%) were intubated in the ED. Regarding the disposition, approximately 40% needed ward admission, and 4% needed ICU admission. The ED mortality rate was low (0%). Lung ultrasound was reported in one study.[17] In this cohort of 12 patients, all exhibited a diffuse B-pattern with spared areas, when 3 patients had posterior subpleural consolidations.

Meta-analysis of patients who tested positive versus negative for COVID-19

The meta-analysis comparing the characteristics, investigation, management and outcomes of COVID-19-positive versus COVID-19-negative patients in the emergency de-partment is shown in table 2. The patients' characteristics did not differ between groups, except for diabetes mellitus which increased the risk of COVID-19 positivity (pooled risk ratio 1.63 (95% CI 1.31–2.05)). Patients who had a history of sick contact or recent travel had a higher risk of testing positive for COVID-19 with pooled risk ratio 2.89 (1.19–7.03) and 3.56 (1.70–7.54) respectively. Clinical manifestations that increased the risk of COVID-19 positivity included decreased taste or smell (pooled risk ratio 6.20 (1.82–21.14), diarrhea (pooled risk ratio 4.02 (1.01–16.09)), shortness of breath (pooled risk ratio 1.52 (1.31–1.77)), and cough (pooled risk ratio 1.72 (1.46–2.02)). Slightly higher body temperature (mean difference 0.27 (95% CI 0.16–0.38) degrees Celsius) and lower systolic blood pressure (mean difference -3.94 (95% CI -5.61 to -2.26 mmHg)) were found in COVID-19 patients than in COVID-19-negative patients. Patients

Table 2 Meta-analysis comparing characteristics, investigation, management and outcomes of COVID-19-positive patients versus COVID-19-negative patients in the emergency department.

Variables	Number of studies	Number of reported patients	Point estimate in COVID-19 positive patients (95%CI)	n	Point estimate in COVID-19 negative patients	n	Effect size (mean difference or risk ratio) and 95%CI (COVID-19 positive compared with COVID-19 negative patients)	I² (%)
Age (years old)	4	3460	50.63 (49.81 – 51.45)	1799	48.97 (48 – 49.94)	1661	Mean difference 2.93 (1.62 – 4.24)	0
Sex: Fe-male(%)	6	3847	45% (42 - 47)	1895	54% (52-56)	1952	Risk ratio 0.58 (0.34 – 1)	76.7
Emergency severity index 1-2	2	1046	5 (0-10%)	80	12 (10-14)	966	Risk ratio 0.43 (0.15 – 1.21)	0
Emergency severity index 3-5	2	523	90 (81 – 99)	40	76 (72-80)	483	Risk ratio 2.48 (0.86 – 7.17)	0
Ethnicity: White (%)	2	3180	43 (40 – 45)	1680	63 (60 – 65)	1500	Risk ratio 0.80 (0.19 – 3.39)	91.53
Ethnicity: Asian (%)	2	3180	3 (3-4)	1680	6 (5-7)	1500	Risk ratio 0.58 (0.41 – 0.83)	0
Ethnicity: Hispanic (%)	2	3180	36 (34 – 38)	1680	17 (15 – 19)	1500	Risk ratio 1.54 (0.41 – 6.17)	83.54
Comorbidity (%)								
COPD	2	3013	4 (3-4)	1683	5 (4-7)	1330	Risk ratio 0.65 (0.46 – 0.92)	0
Smoker	2	243	23 (10-35)	40	27 (21-33)	203	Risk ratio 1.30 (0.55 – 3.06)	0
HT	3	3185	28 (26 – 30)	1694	29 (16-41)	1491	Risk ratio 1.17 (0.99 – 1.38)	0
DM	3	3176	15 (14 – 17)	1694	13 (6-20)	1482	Risk ratio 1.63 (1.31 – 2.05)	0
Malignancy	3	3180	4 (3-5)	1694	8 (3-13)	1486	Risk ratio 0.63 (0.32 – 1.26)	18.33
CVD	3	3192	7 (6-9)	1694	17 (4-31)	1498	Risk ratio 0.70 (0.55 – 0.91)	0
Current smoker (%)	2	243	23 (10-35)	40	27 (21-33)	203	Risk ratio 1.30 (0.55 – 3.06)	0

Table 2 Meta-analysis comparing characteristics, investigation, management and outcomes of COVID-19-positive patients versus COVID-19-negative patients in the emergency department. (Ext.)

Variables	Number of studies	Number of reported patients	Point estimate in COVID-19 positive patients (95%CI)	n	Point estimate in COVID-19 negative patients	n	Effect size (mean difference or risk ratio) and 95%CI (COVID-19 positive compared with COVID-19 negative patients)	I² (%)
Exposure: sick contact (%)	5	3578	45 (42-49)	1753	24 (7-40)	1825	Risk ratio 2.89 (1.19 – 7.03)	87.48
Exposure: travel (%)	4	689	30 (12 – 48)	103	11 (4-17)	586	Risk ratio 3.56 (1.70 – 7.54)	40.80
Clinical manifestation								
Average day symptom to presentation ED (day)	2	356	5.39 (4.58 – 6.19)	43	3.84 (3.31- 4.37)	313	Mean difference 3.89 (-2.64 to 10.43)	91.51
Fever (%)	4	3490	53 (14 – 91)	1721	45 (19-70)	1769	Risk ratio 1.78 (0.87 – 3.62)	57.57
Cough (%)	3	3207	75 (67- 83)	1692	62 (54 – 70)	1515	Risk ratio 1.72 (1.46 – 2.02)	0
Decreased taste/ smell (%)	2	801	21(8-35)	37	3 (2-5)	764	Risk ratio 6.20 (1.82 – 21.14)	26.27
Shortness of breath (%)	2	3081	46 (43 – 48)	1661	39 (36 – 41)	1420	Risk ratio 1.52 (1.31 – 1.77)	0
Fatigue (%)	3	3113	14 (12 – 16)	1692	25 (6-44)	1421	Risk ratio 1.77 (0.67 – 4.68)	52.60
Diarrhea (%)	3	3152	25 (6-43)	1693	9 (0-18)	1459	Risk ratio 4.02 (1.01 – 16.09)	69.12
Physical examination								
SpO2 (%)	2	3137	95.31 (95.05 – 95.58)	1662	97.18 (97.03 – 97.34)	1475	Mean difference -1.353 (-3.039 to 0.333)	55.96

Table 2 Meta-analysis comparing characteristics, investigation, management and outcomes of COVID-19-positive patients versus COVID-19-negative patients in the emergency department. (Ext.)

Variables	Number of studies	Number of reported patients	Point estimate in COVID-19 positive patients (95%CI)	n	Point estimate in COVID-19 negative patients	n	Effect size (mean difference or risk ratio) and 95%CI (COVID-19 positive compared with COVID-19 negative patients)	I² (%)
Heart rate (/min)	2	3013	94.45 (92.38 – 96.53)	1683	85.32 (83.21 – 87.43)	1330	Mean difference -0.68 (-11.38 to 10.01)	38.92
Respiratory rate (/min)	2	3013	19.96 (19.69 – 20.23)	1683	19.42 (19.14 – 19.69)	1330	Mean difference 0.60 (-0.18 to 1.39)	63.36
Body temperature (Degree Celsius)	3	3253	37.38 (37.32 – 37.4)	1694	36.99 (36.91 -37.06)	1559	Mean difference 0.27 (0.16 – 0.38)	0
Systolic blood pressure (mmHg)	2	3137	132.04 (130.98 – 133.10)	1662	136.34 (135.08 – 137.59)	1475	Mean difference -3.94 (-5.61 to -2.26)	0
Investigation								
WBC (/1,000 uL)	4	1829	7.18 (6.91 – 7.44)	957	8.31 (7.96 – 8.65)	872	Mean difference -2.61 (-3.93 to -1.30)	78.61
Leukocytosis (%)								
Neutrophil (1,000/uL)	2	272	4.39 (3.99 – 4.78)	126	4.71 (4.27 – 5.16)	146	Mean difference -1.50 (-3.18 to 0.179)	80.19
Lymphocyte (1,000/uL)	2	272	1.12 (0.99 to 1.25)	126	1.50 (1.39 – 1.61)	146	Mean difference - 0.39 (-0.57 to -0.21)	0
Lymphocyte percentage	2	1349	15.91 (15.22 – 16.61)	829	18.67 (17.59 to 19.74)	520	Mean difference -1.52 (-2.77 to – 0.27)	0

Table 2 Meta-analysis comparing characteristics, investigation, management and outcomes of COVID-19-positive patients versus COVID-19-negative patients in the emergency department. (Ext.)

Variables	Number of studies	Number of reported patients	Point estimate in COVID-19 positive patients (95%CI)	n	Point estimate in COVID-19 negative patients	n	Effect size (mean difference or risk ratio) and 95%CI (COVID-19 positive compared with COVID-19 negative patients)	I² (%)
Platelet count (1,000/uL)	3	457	207.52 (195.64 – 219.40)	204	241.23 (232.04 – 250.42)	253	Mean difference -18.76 (-51.34 to 13.82)	75.38
LDH (U/L)	3	1321	336.34 (354.84 – 377.84)	854	232.57 (221.04 – 244.11)	467	Mean difference 88.51 (51.66 – 125.35)	73.47
CRP (mg/dl)	4	1663	10.32 (9.72 – 10.91)	931	6.17 (5.57 – 6.78)	732	Mean difference 3.12 (2.13 – 4.10)	0
Imaging (%)								
Total CXR	2	3137	58 (55-60)	1662	57 (54-59)	1475	Risk ratio 1.29 (1.11 – 1.50)	0
CXR: Normal	2	1819	27 (25-30)	972	67 (64-70)	847	Risk ratio 0.30 (0.07 – 1.27)	80.66
CXR: Bilateral infiltration	2	1783	60(57-63)	954	19(17-22)	829	Risk ratio 4.16 (1.90 – 9.12)	43.72
Total CT chest	3	3253	38 (0-100)	1694	48 (7-90)	1559	Risk ratio 0.77 (0.63 – 0.95)	0
CT chest: Normal	2	467	11 (8-16)	227	53(47-59)	240	Risk ratio 0.15 (0.03 – 0.68)	22.92
CT chest: Bilateral infiltration	2	555	81(77-86)	259	32(27-38)	296	Risk ratio 9.27 (6.15 – 13.99)	0
Management (%)								
Intubation in the ED	2	2925	8 (7-10)	1502	3(2-4)	1423	Risk ratio 3.59 (1.48 – 8.69)	14.16

Table 2 Meta-analysis comparing characteristics, investigation, management and outcomes of COVID-19-positive patients versus COVID-19-negative patients in the emergency department. (Ext.)

Variables	Number of studies	Number of reported patients	Point estimate in COVID-19 positive patients (95%CI)	n	Point estimate in COVID-19 negative patients	n	Effect size (mean difference or risk ratio) and 95%CI (COVID-19 positive compared with COVID-19 negative patients)	I^2 (%)
Disposition (%)								
Discharge	3	3420	43 (12-78)	1691	42 (5-86)	1729	Risk ratio 0.89 (0.37 – 2.19)	62.74
Admission	3	3420	28 (20 – 57)	1691	40 (24-55)	1729	Risk ratio 1.14 (0.56 – 2.31)	62.48
Ward	2	3137	41 (39- 43)	1662	31 (29 – 34)	1475	Risk ratio 1.41 (0.65 – 3.06)	51.36
ICU	2	3137	4 (3-4)	1662	4 (3-5)	1475	Risk ratio 1.04 (0.7 – 1.53)	0
Final outcome* (%)								
Mortality in ED	2	3137	0 (0-0)	1662	0 (0-0)	1475	Risk ratio 2.80 (0.66 – 11.76)	0
In-hospital mortality	2	3137	3 (2-4)	1662	2 (1-3)	1475	Risk ratio 2.52 (1.57 – 4.06)	0

BT: Body temperature; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: Computed tomography; CXR: Chest X-ray; ED: Emergency department; HR: Heart rate; HT: Hypertension; ICU: Intensive care unit; LDH: Lactate dehydrogenase; LOS: length of stay; RR: Respiratory rate; SBP: Systolic blood pressure; SpO2: Oxygen saturation; WBC: White blood cell count

*Data for the final clinical outcome are not available for all patients as some of them were still hospitalized at the time of publication.

with COVID-19 generally had lower average leukocyte counts (mean difference -2.61 (-3.93 to -1.30) 1000/μL), lower lymphocyte counts with (mean dif-ference - 0.39 (95% CI -0.57 to -0.21) 1000/μL), lower lymphocyte percentages (mean dif-ference -1.52 (95% CI -2.77 to – 0.27), higher LDH mean differences (88.51 (95% CI 51.66–125.35) U/L) and higher CRP levels (mean difference 3.12 (95% CI 2.13–4.10) mg/dl). Bilateral infiltration in chest X-ray (CXR) and chest computed tomography (Chest CT) increased the risk of testing positive for COVID-19 with pooled OR 4.16 (1.90–9.12) and OR 9.27 (6.15–13.99), respectively. Having COVID-19 positivity increased the risk of intubation in the ED, with pooled OR of 3.59 (1.48–8.69). No difference in disposition or ED mortality was found between the two groups.

Case reports and case series

A quantitative summary of 40 case reports is shown in table[22-61], and 14 case series are shown in table.[62-75] The details and methodological quality of the case report and case series are described in table S2-3 (available in the supplementary file). Many COVID-19 patients present to the ED with non-respiratory symptoms, such as gastrointestinal (GI) symp-toms, neurologic deficits, skin rash, or unspecific symptoms, such as fatigue and muscle aches. Fever and respiratory symptoms may be observed concurrently with other abnormali-ties or present later. Some patients never develop respiratory symptoms through the clinical course of infection.

We summarize the three atypical manifestations of COVID-19 including gastrointestinal, neurological, and dermatological.

Gastrointestinal manifestations and complications of COVID-19

Patients with COVID-19 infection often have GI symptoms, including diarrhea, nau-sea, vomiting and abdominal pain. According to our systematic review, GI manifestations are secondary only to respiratory tract symptoms, with diarrhea as the most common symptom. Most patients with GI involvement are found to have concurrent fever and cough. However, abdominal pain alone is also reported in some confirmed COVID cases, and most GI symp-toms completely resolve after supportive care and antiviral therapy.[34, 67, 71, 72]

Table 3   Summary measures of data from case reports showing characteristics, investigation, management and outcomes of patients with COVID-19

Variable	Number of case reports with available data	Total population	Estimates
Median age in years (IQR)	40	40	47 (22.5)
Sex: Female (%)	40	13 (33)	13 (33%)
Presence of comorbidity (%)	36	22	22 (61%)
Asthma		3	3 (8%)
COPD		2	2 (6%)
HT		11	31%
Diabetes mellitus		10	28%
Dyslipidemia		8	22%
CKD		2	6%
Malignancy		2	6%
Cardiac diseases		6	17%
Exposure: travel (%)	34	7	21%
Exposure: sick contact(%)	33	8	24%
Average day of symptom onset to ED (%)	40	40	6
Clinical manifestation (%)			
Fever	38	27	71%
Cough	36	22	61%
Sore throat	17	4	24%
Rhinorrhea/congestion	15	2	13%
Shortness of breath	34	18	53%
Fatigue	15	11	73%
Diarrhea	13	3	23%
Nausea/vomiting	13	6	46%
Abdominal pain	13	5	38%
Chest pain	12	5	42%

Table 3 Summary measures of data from case reports showing characteristics, investigation, management and outcomes of patients with COVID-19 (Ext.)

Variable	Number of case reports with available data	Total population	Estimates
Physical examination (%)			
Hypoxia (SpO2 < 95% breathing room air)	38	23	61%
Tachycardia (>100/min)	28	13	46%
Tachypnea (>20/min)	23	9	39%
Hypotension (Systolic blood pressure <90 mmHg)	24	3	13%
Fever (Body temperature > 38 ℃)	38	23	61%
Laboratory investigation (%)			
CBC (abnormal results are interpreted based on local reference range)			
Anemia (Hb <11 mg/dL)	18	2	11%
Leukocytosis(>11,000/uL)	30	8	27%
Leukopenia (<4,000/uL)	30	3	10%
Neutrophilia (>7500/uL)	27	4	15%
Neutropenia (<1500/uL)	27	0	0%
Lymphocytosis (>4,000/uL)	27	0	0%
Lymphopenia (<4300/uL)	27	15	56%
Thrombocytopenia (<150,000/uL)	20	5	25%
Elevated CRP (>3 mg/dl)	20	17	85%
Procalcitonin (>0.5ng/mL)	7	3	43%
Elevated LDH (>190 U/L)	10	8	80%
Elevated Ferritin (> 250 ng/mL)	6	6	100%
Others (%)			
Lactate (> 2 mg/dL)	8	4	50%

Table 3   Summary measures of data from case reports showing characteristics, investigation, management and outcomes of patients with COVID-19 (Ext.)

Variable	Number of case reports with available data	Total population	Estimates
Elevated CK (> 200 U/L)	5	4	80%
Detection of influenza	14	0	0%
Imaging (%)			
Total CXR	40	27	68%
CXR: Bilateral infiltration	10	37%	
CXR: Unilateral infiltration	7	26%	
CXR: No infiltration	9	33%	
Total Chest CT	40	29	73%
CT chest: Bilateral ground grass opacity	26	90%	
CT chest: Unilateral opacity		3	10%
CT chest: Pulmonary embolism		5	17%
CT chest: Negative study		0	0%
Positive Chest CT study with normal CXR		4	14%
Management (%)			
Intubation in the ED	40	5	12.5%
Disposition (%)			
Discharge	40	5	12.5%
Admit Ward	40	22	55%
Admit ICU	40	13	33%
Final outcome* (%)			
Mortality in ED	28	1	3.5%
In-hospital mortality	28	7	25%

BT: Body temperature; CK: Creatinine kinase; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: Computed tomography; CXR: Chest X-ray; ED: Emergency department; HT: Hypertension; ICU: Intensive care unit; IQR: interquartile range; LDH: Lactate dehydrogenase; SpO2: Oxygen saturation; WBC: White blood cell count, *Data for the final clinical outcome are not available for all patients as some of them were still hospitalized at the time of publication.

Neurological manifestations and complications of COVID-19

Neurological complications in hospitalized patients with COVID-19 are not uncommon.[29, 37, 62] The most commonly reported symptoms include headache, dizziness and altered mental status. However, these symptoms without focal neurologic deficits are nonspecific and can generally be observed in patients with any viral infection and fever in the absence of demonstrable brain lesions.

A case report by Gonzalez et al. described a 36-year-old female presenting to the ED with altered mental status and hemiparesis from Lt internal carotid artery occlusion. Chest CT revealed bilateral PE and thrombus in the ascending aorta. No respiratory tract symptoms or fever were documented in this patient. A SARS-CoV-2 nasal swab was per-formed due to imaging findings, and the test returned a positive result.[37]

Another case report by Co COC et al. showed a 61-year-old female who presented to the ED with symptoms of Lt MCA infarction. She developed fever and cough 2 weeks prior, and chest CT again showed bilateral lung infiltration.[29]

A case series by Avula et al. described 4 patients, with an average age of 81 years and with multiple comorbidities, who visited the ED and were diagnosed with large vessel stroke and COVID-19 infection; 3 of them had fever, dyspnea and desaturation. Chest CT typical findings of peripheral infiltration.[62]

Skin manifestations and complications of COVID-19

Fever and skin rash were also symptoms of ED patients. Hunt et al. made the first case report regarding rash in COVID-19 patients. A young male was initially diagnosed with a viral upper respiratory tract infection and, six days later, developed diffuse morbilliform, maculopapular (MP) rash and worsening respiratory symptoms at the ED.[41] Another report by Amatore et al. also described an infected male patient with fever and annular fixed plaques involving the upper limbs, palms and torso, but he had no respiratory tract symptoms. Chest CT was performed in both, showing bilateral and peripheral ground-glass opacity, imaging findings typically found in COVID patients.[24] Skin rash as the sole manifestation of COVID infection is possible, as reported by Quintana-Castanedo et al. describing an

elderly nonfebrile patient coming to the ED with urticarial rash on both limbs sparing palms and soles.[56] More data about the characteristics of rash are necessary to find common patterns of skin involvement, but these reports highlight the need for differential diagnosis of COVID-19 infection and early isolation when encountering patients with unexplained rash, regardless of fever or respiratory symptoms, in the era of COVID-19.

Discussion

This systematic review and meta-analysis described the clinical manifestation, investigation, management and outcomes of patients with COVID-19. Patients typically presented with a history of sick contact or recent travel. Cough, fever and shortness of breath were the most common chief complaints. Although rarely present in ED patients, decreased taste and smell significantly increased the probability of COVID-19 diagnosis. Several rare clinical presentations of COVID-19 include stroke and skin rashes. Gastrointestinal symptoms were found in up to 10-20% of the patients. Although initial vital signs were not different between those who tested positive and negative

for COVID-19, the intubation rate in the ED was tripled in those with COVID-19. Notable investigations were lymphopenia and bilateral infiltration on chest imaging. Undoubtedly, the patients with COVID-19 most common presented to the emergency department with respiratory symptoms, such as cough, fever and shortness of breath Inter-estingly, although in the emergency department, patients mostly did not present with notice-able hypoxemia. The average SpO_2 on presentation was 95%. This is similar to large cohort studies reported after this systematic review.[76] Common X-ray findings included bilateral infil-tration. However, abnormal X-ray findings are not adequately sensitive to be used as an ef-fective screening tool for COVID-19 infection. Chest CT is generally not part of routine initial investigations in the emergency department, although it is more sensitive in the diagnosis of COVID-19 pneumonia.[77] Moreover, it can convey the risk of viral contamination and is con-sidered an intricate, time-consuming investigation.[78] The rapid antigen test is a new feasible option for the rapid detection of COVID-19 infection.[79]

Gastrointestinal symptoms, especially

Table 4 Summary measures of data from case series showing characteristics, investigation, management and outcomes of patients with COVID-19

Variables	Number of studies	Number of total patients	Number of report patients	Estimates
Median age in years (IQR)	14	63	41	69(26)
Sex: Female (%)	14	63	29	46%
Having comorbidity (%)	10	39	9	90%
Clinical manifestation (%)				
Fever (Body temperature > 38.0 C)	13	59	42	71%
Hypoxia (SpO2 < 96%)	14	63	42	67%
Respiratory symptoms*	14	63	30	48%
GI symptoms†	12	43	12	30%
Neurological symptoms‡	3	8	4	50%
Blood tests (%)				
Anemia (Hb <11 mg/dL)	5	13	3	26%
Leukocytosis (>11,000/uL)	10	35	6	17%
Leukopenia (<4,000/uL)	10	35	6	17%
Neutrophilia (>7500/uL)	10	35	6	17%
Neutropenia (<1500/uL)	10	35	2	6%
Lymphocytosis (>4,000/uL)	10	35	0	0
Lymphopenia (<4300/uL)	10	35	18	51%
Thrombocytopenia (<150,000/uL)	7	26	6	23%
Others (%)				
Elevated LDH (>190 U/L)	4	16	15	94%
Elevated CRP (>3 mg/dl)	10	28	8	29%
Elevated CK (> 200 U/L)	1	2	2	100%
Elevated D-dimer (> 500 ng/mL)	7	15	12	80%
Procalcitonin (> 2 ng/mL)	5	12	3	25%
Ferritin (> 250 ng/mL)	4	8	5	63%

Table 4   Summary measures of data from case series showing characteristics, investigation, management and outcomes of patients with COVID-19 (Ext.)

Variables	Number of studies	Number of total patients	Number of report patients	Estimates
Imaging (%)				
Total CXR			13	
CXR: Bilateral patchy opacity			9	69%
CXR: Unilateral opacity			2	15%
Normal CXR study			2	15%
Total Chest CT			36	
CT chest: Bilateral GGO*			32	89%
CT chest: Unilateral opacity			1	3%
CT chest: Pulmonary embolism			1	3%
Normal Chest CT study			1	3%
Chest CT positive findings with normal CXR study			2	5%
Management (%)				
Intubation in the ED	14	63	3	10%
Disposition (%)				
Discharge	14	63	2	3%
Admission	14	63	61	97%
Ward	14	63	47	75%
ICU	14	63	14	22%
Final outcome§ (%)				
Mortality in ED	12	53	0	0%
In-hospital mortality	12	53	8	15%

BT: Body temperature; CK: Creatinine kinase; CRP: C-reactive protein; CT: Computed to-mography; CXR: Chest X-ray; ED: Emergency department; ICU: Intensive care unit; IQR: interquartile range; LDH: Lactate dehydrogenase; SpO2: Oxygen saturation;

*Respiratory symptoms require at least one of the following: cough, shortness of breath, sore throat, rhinorrhea and hemoptysis

†Gastrointestinal symptoms require at least one of the following: diarrhea, vomiting, ab-dominal pain

‡Neurological symptoms require at least one of the following: anosmia, altered mental status, hemiparesis

§*Data for the final clinical outcome are not available for all patients, as some of them were still hospitalized at the time of publication.

diarrhea and abdominal pain, can coexist or be the only manifestation in patients with COVID-19. The ACE-2 receptor, a main target for SARS-CoV-2 entry into human cells, is suspected to play an important role in GI and other organ dysfunction since it is expressed in multiple human tissues, including lungs, liver, kid-neys and intestinal epithelium. Activation of the receptor by this coronavirus can trigger an immune response, resulting in local inflammation and tissue dysfunction in affected organs, including the GI tract.[80] GI symptoms especially abdominal pain have always been a great challenge for ED physicians since they can mimic more common intra-abdominal diseases. In the era of the COVID-19 pandemic, it is advisable to look for abnormal lung infiltration if ab-dominal imaging that includes any part of the lung is performed. Prompt COVID-19 testing should be carried out in any cases with unexplained abnormal lung imaging.

From this review, ischemic stroke was the most common neurological manifestation for ED patients with COVID-19 infection, and respiratory symptoms may or may not be pre-sent.[29,37] More evidence has shown that COVID-19 infection is related to a hypercoagulable state, which might explain the ischemic phenomenon. The pathophysiology behind these events remains uncertain, but it is presumed that this novel virus increases the hypercoagu-lable state through various mechanisms, including cytokine storms, immune-mediated re-sponses, and endothelial dysfunction.[81] Additionally, similar thrombotic disorders have been reported in patients infected with a genetically similar coronavirus named SARS-CoV-1, which caused SARS outbreaks in the early 2000s. Another possible mechanism is viral infec-tion of the CNS causing local inflammatory responses and vessel thrombosis. Although the ACE2 receptor is abundant on epithelial cells lining the respiratory and gastrointestinal tracts, the receptor is also expressed on glial cells.[82] Patients with COVID-19 had thrice the risk of intubation in the ED when compared to those without COVID-19. Since intuba-tion is considered an aerosol-generating procedure, emergency physicians must be familiar with safe intubation to minimize the risk of transmis-sion to health care workers.[83] Many alternatives in the management of hypoxia in COVID-19 include the use of awake prone positioning[11], a high-flow nasal cannula,

and noninvasive ventilation[84], although the optimal timing of intubation remains unclear.[85]

To our knowledge, this is the first systematic review and meta-analysis on COVID-19 patients in the emergency department. We included case reports and case series to capture atypical presentations that were presented by the COVID-19 patients. However, this study had several limitations. Regarding the meta-analysis, for many outcomes, the included studies provided significant heterogeneity. Moreover, due to the paucity of data during the time of search, many outcomes were represented by only 2 studies. Moreover, although we did not limit the search to adults, most of the studies reported only adult patients.

Conclusion

Patients with COVID-19 can present to EDs with several unusual manifestations, including gastrointestinal, neurological and dermatological problems. As the intubation rate tripled in those with COVID-19 compared to those without, emergency providers should prepare for safe intubation in patients suspected to have COVID-19.

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Conflict of interest

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