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SYSTEMATIC REVIEW

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A systematic review of thromboembolic complications and outcomes in hospitalised COVID-19 patients

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Abstract

Thromboembolic (TE) complications [myocardial infarction (MI), stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE)] are common causes of mortality in hospitalised COVID-19 patients. Therefore, this review was undertaken to explore the incidence of TE complications and mortality associated with TE complications in hospitalised COVID-19 patients from different studies. A literature search was performed using ScienceDirect and PubMed databases using the MeSH term search strategy of "COVID-19", "thromboembolic complication", "venous thromboembolism", "arterial thromboembolism", "deep vein thrombosis", "pulmonary embolism", "myocardial infarction", "stroke", and "mortality". There were 33 studies included in this review. Studies have revealed that COVID-19 patients tend to develop venous thromboembolism (PE:1.0-40.0% and DVT:0.4-84%) compared to arterial thromboembolism (stroke:0.5-15.2% and MI:0.8-8.7%). Lastly, the all-cause mortality of COVID-19 patients ranged from 4.8 to 63%, whereas the incidence of mortality associated with TE complications was between 5% and 48%. A wide range of incidences of TE complications and mortality associated with TE complications can be seen among hospitalized COVID-19 patients. Therefore, every patient should be assessed for the risk of thromboembolic complications and provided with an appropriate thromboprophylaxis management plan tailored to their individual needs.

Keywords Venous thromboembolism, Arterial thromboembolism, Myocardial infarction, Stroke, Deep vein thrombosis, Pulmonary embolism, Mortality

Introduction

By the end of 2019, cases of pneumonia of unknown etiology, believed to have been caused by a new coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and later known as COVID-19 disease were discovered [1]. The lung epithelium, myocardium, and vascular endothelium are the major sites where the SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which results in lung and cardiovascular complications [2].

Aside from pulmonary complications, cardiovascular complications such as cardiac injury, heart failure,

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arrhythmia, and atherosclerosis were also reported during the early phases of COVID-19 outbreak [3, 4]. In these cardiovascular complications, endothelial inflammation (endotheliitis) and dysfunction due to the viral infection affected vascular homeostasis and organ perfusion [5]. Endotheliitis is found to be associated with hyperpermeability, vascular endothelial dysfunction, and thrombus formation, eventually resulting in thromboembolic (TE) complications [6].

As more clinical cases emerge, episodes of TE complications, such as arterial thrombosis or venous thrombosis, in hospitalized patients have been widely observed [7]. Deep vein thrombosis (DVT) and pulmonary embolism (PE) characterize venous thromboembolism (VTE) [8], while arterial thromboembolism (ATE) typically manifests as myocardial infarction (MI) or stroke [9].

A cross-sectional study performed in Wuhan, China [10] with a study population of 143 COVID-19 patients reported that approximately half of their hospitalised COVID-19 patients ($n=66$) developed deep vein thrombosis (DVT). Approximately 35% ($n=23/66$) of COVID-19-related deaths were observed among those who developed DVT.

A validated mortality prognostic tool identified a few demographic and clinical risk factors, such as age, male sex, hypertension, and obesity, as risk factors for severe disease progression and death in COVID-19 patients [11]. Advanced age is one of the identified mortality risk factors, and it may be due to a high level of reactive oxygen species that could injure vascular endothelial cells and eventually cause TE complications [12].

Furthermore, hospitalized COVID-19 patients with pre-existing comorbidities such as cardiovascular disease, active cancer, diabetes, or a history of TE complications are more likely to be at risk of developing TE complications and mortality [13]. In this review, we aimed to explore the incidence of TE complications in hospitalized COVID-19 patients and the mortality outcomes associated with TE complications from different studies.

Materials and methods

A literature review was performed using the ScienceDirect and PubMed databases for research articles published. The search strategy was completed using keywords and subject headings related to "COVID-19", "thromboembolic complications", "venous thromboembolism", "arterial thromboembolism", "deep vein thrombosis", "pulmonary embolism", "myocardial infarction", "stroke", and "mortality".

The inclusion criteria of the published articles were based on the study design of observational studies comprising both prospective and retrospective studies that reported on the incidences of TE complications in COVID-19. Meanwhile, the outcome of the studies focused on episodes of venous thromboembolism (deep vein thrombosis and pulmonary embolism) or arterial thromboembolism (myocardial infarction and stroke) and mortality in COVID-19 patients who developed TE complications during hospitalization.

The publication dates included articles published from March 2020 to September 2023. In addition, there was no geographical restriction in the systematic review if the articles were published in English language to ensure the transparency and reliability of all relevant studies. We implemented a SIGN checklist approach to assess the risk of bias in the included study (Table 1).

The exclusion criteria were all irrelevant study design, topics, and outcomes that were not related to hospitalized COVID-19 patients who developed TE complications. Any duplicate publications, or articles that were not published or accessed in the English language were excluded from the screening and eligibility process (Fig. 1).

Based on the keywords used in the database, we found a total of 5,010 research articles. Finally, after the selection of articles based on the inclusion and exclusion criteria, there were 33 studies included in this review regarding the incidence of TE complications and mortality outcomes among hospitalized COVID-19 patients.

Results

Most of the included studies have been performed in Europe ($n=18$) [14, 17–20, 22, 23, 25–27, 33–36, 39, 43, 44, 46], the United States of America (USA) ($n=9$) [15, 29–32, 38, 40, 41, 45], Asia ($n=2$) [21, 42], North Africa ($n=2$) [16, 24] and the United Kingdom [28, 37]. The majority of the studies were conducted retrospectively ($n=27$) [15–18, 22–42, 44, 46], whereas only six studies were conducted prospectively [14, 19–21, 43, 45]. All study participants were hospitalized with COVID-19 patients, ranging from 23 [21] to 5,966 [34] patients. These studies included patients who were admitted to the intensive care unit (ICU) ($n=8$) [14, 18, 27, 28, 32, 33], general wards ($n=12$) [16, 19–21, 29, 30, 35, 36, 38, 40, 41, 45] or a combination of both the ICU and general wards ($n=13$) [15, 17, 22–26, 31, 34, 37, 39, 42, 44] (Table 2).

Incidence of TE complications in hospitalized COVID-19 patients

Fourteen studies reported both the incidence of VTE (PE and/or DVT) and ATE (stroke and/or MI) in their study population [14–18, 22, 23, 25, 32, 43–47]. Twenty-seven studies [14–18, 20, 22–26, 28, 29, 31, 32, 34–39, 41–46] reported the incidence of PE ranging from 1.0% [41] to 57% [35] with the lowest reported in the USA and the highest in Europe. Patients admitted to the general ward had the highest incidence of PE at 57% [35], followed by

Table 1 Summary risk of bias assessment for each included study based on SIGN checklist: cohort study

Studies	PICO	Section 1: Internal Validity														Section 2: Overall Assessment of the Study		
		S1.1	S1.2	S1.3	S1.4	S1.5	S1.6	S1.7	S1.8	S1.9	S1.10	S1.11	S1.12	S1.13	S1.14	S2.1	S2.2	S2.3
Klok, Kruip [14]	Yes	Yes	Yes	Yes	Not applicable	Can't say	Yes	Yes	No	No	Yes	Yes	Can't say	Yes	Yes	Acceptable	Yes	Yes
Al-Samkari, Karp Leaf [15]	Yes	Yes	Yes	Yes	Yes	Can't say	Yes	Yes	Not applicable	No	Yes	Yes	Can't say	Yes	Yes	Acceptable	Yes	Yes
Mohamud and Mukhtar [16]	Yes	Yes	Yes	Yes	No	Can't say	Not applicable	Yes	Not applicable	Can't say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Kaptein, Stals [17]	Yes	Yes	Yes	Yes	No	Can't say	Not applicable	Yes	Can't say	Can't say	Yes	Yes	Can't say	Yes	Yes	Acceptable	Can't say	Yes
Gonzalez-Fajardo, Ansuategui [18]	Yes	Yes	Not applicable	Not applicable	Can't say	Can't say	Not applicable	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Jimenez-Guiu, Huici-Sanchez [19]	Yes	Yes	Yes	Yes	Yes	Can't Say	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High Quality	Yes	Yes
García-Ortega, Oscullo [20]	Yes	Yes	Yes	Yes	Not applicable	Can't Say	Not applicable	Yes	No	No	Yes	Yes	Can't say	Yes	Yes	Acceptable	Yes	Yes
Chen, Jiang [21]	Yes	Yes	Yes	Yes	Not applicable	Can't say	Not applicable	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Martinot, Eyriey [22]	Yes	Yes	Not applicable	Yes	Yes	Can't say	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Munoz-Rivas, Abad-Motos [23]	Yes	Yes	Not applicable	Yes	Can't say	Can't say	Not applicable	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Kajoak, Osman [24]	Yes	Yes	Yes	Yes	No	Can't say	Not applicable	Yes	Not applicable	No	Yes	Yes	Can't say	Yes	Yes	Acceptable	Yes	Yes
Tholin, Fiskvik [25]	Yes	Yes	Yes	Yes	No	Can't say	Yes	Yes	Not applicable	Can't say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Martínez Chamorro, Revilla Ostolaza [26]	Yes	Yes	Yes	Yes	Can't Say	Can't say	Not applicable	Yes	Not applicable	No	Yes	Yes	Can't say	Yes	Yes	Acceptable	Yes	Yes
Bozzani, Arici [27]	Yes	Yes	Yes	Not applicable	Not applicable	Can't say	Not applicable	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Elboushi, Syed [28]	Yes	Yes	Yes	Yes	Can't Say	Can't Say	No	Yes	Not applicable	No	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Rali, O'Corragain [29]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Not applicable	No	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Erben, Franco-Mesa [30]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Filippi, Sartori [31]	Yes	Yes	Yes	Yes	Can't Say	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Brandao, de Oliveira [32]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Haksteen, Hilderink [33]	Yes	Yes	Yes	Yes	Can't Say	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes

Table 1 (continued)

Studies	PICO	Section 1: Internal Validity														Section 2: Overall Assessment of the Study		
		S1.1	S1.2	S1.3	S1.4	S1.5	S1.6	S1.7	S1.8	S1.9	S1.10	S1.11	S1.12	S1.13	S1.14	S2.1	S2.2	S2.3
Arribalzaga, Martinez-Alfonzo [34]	Yes	Yes	Yes	Yes	Can't Say	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Valle, Bonaffini [35]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Silva, Jorge [36]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Whyte, Kelly [37]	Yes	Yes	Yes	Yes	Can't Say	Can't Say	Not applicable	Yes	Not applicable	Can't Say	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Vivan, Rigatti [38]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Not applicable	No	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Bruggemann, Spaetgens [39]	Yes	Yes	Yes	Yes	No	Can't Say	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Chang, Rockman [40]	Yes	Yes	Yes	Yes	Yes	Can't Say	Not applicable	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Chaudhary, Padrnos [41]	Yes	Yes	Yes	Yes	Yes	Can't Say	Not applicable	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Fujiwara, Nakajima [42]	Yes	Yes	Not Applicable	Yes	Not Applicable	Can't Say	Yes	Yes	Not Applicable	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Helms, Tacquard [43]	Yes	Yes	Yes	Yes	Yes	Can't say	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Lodigiani, Iapichino [44]	Yes	Yes	Not applicable	Yes	Can't say	Can't say	Not applicable	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes

Table 1 (continued)

Studies	PICO	Section 1: Internal Validity														Section 2: Overall Assessment of the Study		
		S1.1	S1.2	S1.3	S1.4	S1.5	S1.6	S1.7	S1.8	S1.9	S1.10	S1.11	S1.12	S1.13	S1.14	S2.1	S2.2	S2.3
Cueto-Robledo, Navarro-Vergara [45]	Yes	Yes	Not applicable	Yes	Can't say	Can't say	Not applicable	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes
Fraissé, Logre [46]	Yes	Yes	Not applicable	Yes	Can't say	Can't say	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable	Yes	Yes

Domain:

S1.1: The study addresses an appropriate and clearly focused question

S1.2: The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation

S1.3: The study indicates how many of the people asked to take part did so, in each of the groups being studied

S1. 4: The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis

S1.5: What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed

S1.6: Comparison is made between full participants and those lost to follow up, by exposure status

S1.7: The outcomes are clearly defined

S1.8: The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable

S1.9: Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome

S1.10: The method of assessment of exposure is reliable

S1.11: Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable

S.12: Exposure level or prognostic factor is assessed more than once

S.13: The main potential confounders are identified and taken into account in the design and analysis.

S.14: Have confidence intervals been provided?

S2.1: How well was the study done to minimise the risk of bias or confounding?

S2.2: Considering clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?

S3.3: Are the results of this study directly applicable to the patient group targeted in this guideline?

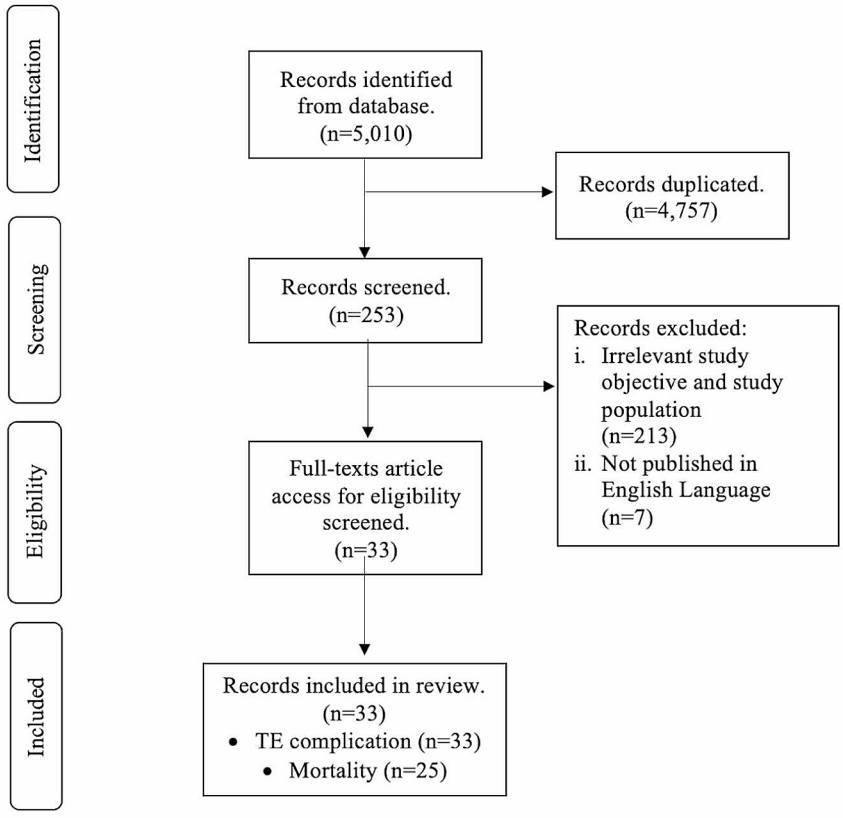

Fig. 1 PRISMA flowchart on study selection

those in the ICU and general ward at 40% [39], and those admitted to the ICU alone at 22.2% [18] (Table 2).

Among the 22 studies [14–19, 21–23, 25, 27–29, 32, 34, 40–46] included, DVT was seen among 0.4% (n=21/5966) [34] to 84.2% (n=32/38) [27] of COVID-19 patients seen in European studies. Critically ill patients in the ICU had the highest incidence of 84.2% (n=32/38), followed by 82.6% (n=19/23) in the general ward population [21] and 2.3% (n=9/400) in the combination of the ICU and general ward [15] (Table 1). According to two articles that observed both PE and DVT, the current incidence of VTE was approximately 9.0% (n=82/915) [30] in the COVID-19 population and increased five-fold (n=81/188) [33] in severely ill COVID-19 patients (Table 2).

Twelve studies specifically reported the incidence of both VTE and ATE in their study population [15–18, 23, 25, 32, 41, 43–46]. Although one study [16] showed a higher incidence of ATE [stroke:15.2% and MI:8.7%] than VTE [PE:13.0% and DVT:4.3%], other studies (n=11) showed that VTE was more common than ATE, with the incidence of PE [1.0% [41] to 34.6% [45] and DVT [0.5% [23] to 7.7% [18] compared to stroke [0.5% [15] to 15.2% [16] and MI [0.5% [23] to 8.7% [16].

Fourteen studies reported the incidence of MI and stroke in a hospitalized COVID-19 population [14–18, 22, 23, 25, 32, 41, 43–46]. The incidence of MI ranged from 0.5% (n=6/1127) [23] to 8.7% (n=4/46) [16] with lower rates observed in European studies (0.5-5.0%) [18, 23].

Meanwhile, studies conducted in North Africa, Europe, and the USA revealed that the current incidence of stroke in COVID-19 patients varied between 0.5% (n=2/400) [15] and 15.2% (n=7/46) [16] with Americans having the lowest incidence (0.5–3.8%) [15, 45] (Table 2). Patients admitted to general COVID-19 wards commonly experienced both events, with the North African population having the highest incidences of both stroke and MI (Table 2).

Outcomes in COVID-19 patients associated with TE complications

In this review, three main outcomes for every hospitalized COVID-19 patient were investigated: discharge, being still hospitalized, and death. To standardize the second outcome in all studies, patients who continued to be in the ICU or general ward, transferred to the general ward from the ICU, or transferred to another hospital were classified as "still hospitalized".

Table 2 Summary of literature included for epidemiology of TE complications among hospitalised COVID-19 patients

No.	First Author Location	Study Design No. of sample	Study Setting	Venous Thromboembolism		Arterial Thromboembolism	
				PE	DVT	Stroke	MI
1.	Klok, Kruip [14] Netherlands (Europe)	Prospective 184	ICU	13.6% (*n* = 25)	1.6% (*n* = 3)	1.6% (*n* = 3)	-
2.	Al-Samkari, Karp Leaf [15] USA	Retrospective 400	ICU and General Ward	2.5% (*n* = 10)	2.3% (*n* = 9)	0.5% (*n* = 2)	2.3% (*n* = 9)
3.	Mohamud and Mukhtar [16] Somalia (North Africa)	Retrospective 46	General ward	13.0% (*n* = 6)	4.3% (*n* = 2)	15.2% (*n* = 7)	8.7% (*n* = 4)
4.	Kaptein, Stals [17] Netherlands (Europe)	Retrospective 947	ICU and General Ward	10.2% (*n* = 97)	0.7% (*n* = 7)	1.3% (*n* = 12)	0.8% (*n* = 8)
5.	Gonzalez-Fajardo, Ansuategui [18] Spain (Europe)	Retrospective 261	ICU	22.2% (*n* = 58)	7.7% (*n* = 20)	5.7% (*n* = 15)	5.0% (*n* = 13)
6.	Jimenez-Guiu, Huici-Sanchez [19] Spain (Europe)	Prospective 57	General ward	-	10.5% (*n* = 6)	-	-
7.	García-Ortega, Oscullo [20] Spain (Europe)	Prospective 73	General ward	35.6% (*n* = 26)	-	-	-
8.	Chen, Jiang [21] China (Asia)	Prospective 23	General ward	-	82.6% (*n* = 19)	-	-
9.	Martinot, Eyriey [22] France (Europe)	Retrospective 600	ICU and General Ward	2.7% (*n* = 16)	2.2% (*n* = 13)	-	1.3% (*n* = 8)
10.	Munoz-Rivas, Abad-Motos [23] Spain (Europe)	Retrospective 1127	ICU and General Ward	3.9% (*n* = 44)	0.5% (*n* = 6)	1.2% (*n* = 13)	0.5% (*n* = 6)
11.	Kajoak, Osman [24] Saudi Arabia (North Africa)	Retrospective 445	ICU and General Ward	8.1% (*n* = 36)	-	-	-
12.	Tholin, Fiskvik [25] Norway (Europe)	Retrospective 550	ICU and General Ward	3.6% (*n* = 20)	0.6% (*n* = 3)	0.7% (*n* = 4)	2.0% (*n* = 11)
13.	Martínez Chamorro, Revilla Ostolaza [26] Spain (Europe)	Retrospective 342	ICU and General Ward	26% (*n* = 89)	-	-	-
14.	Bozzani, Arici [27] Italy (Europe)	Retrospective 38	ICU	-	84.2% (*n* = 32)	-	-
15.	Elboushi, Syed [28] UK	Retrospective 198	ICU	14.6% (*n* = 29)	7.6% (*n* = 15)	-	-
16.	Rali, O'Corragain [29] USA	Retrospective 147	General ward	10.9% (*n* = 16)	9.5% (*n* = 14)	-	-
17.	Erben, Franco-Mesa [30] USA	Retrospective 915	General ward	9.0% (*n* = 82)		-	-
18.	Filippi, Sartori [31] USA	Retrospective 267	ICU and General Ward	18.7% (*n* = 50)	-	-	-
19.	Brandao, de Oliveira [32] Brazil (USA)	Retrospective 243	ICU	7.8% (*n* = 19)	3.7% (*n* = 9)	1.2% (*n* = 3)	2.5% (*n* = 6)
20.	Haksteen, Hilderink [33] Netherlands (Europe)	Retrospective 188	ICU	43.1% (*n* = 81)		-	-

Table 2 (continued)

No.	First Author Location	Study Design No. of sample	Study Setting	Venous Thromboembolism		Arterial Thromboembolism	
				PE	DVT	Stroke	MI
21.	Arribalzaga, Martinez-Alfonzo [34] Spain (Europe)	Retrospective 5966	ICU and General Ward	2.6% (*n* = 176)	0.4% (*n* = 21)	-	-
22.	Valle, Bonaffini [35] Italy (Europe)	Retrospective 114	General ward	57% (*n* = 65)	-	-	-
23.	Silva, Jorge [36] Portugal (Europe)	Retrospective 300	General ward	15.3% (*n* = 46)	-	-	-
24.	Whyte, Kelly [37] UK	Retrospective 214	ICU and General Ward	37.4% (*n* = 80)	-	-	-
25.	Vivan, Rigatti [38] Brazil (USA)	Retrospective 697	General ward	32.4% (*n* = 226)	-	-	-
26.	Bruggemann, Spaetgens [39] Netherlands (Europe)	Retrospective 60	ICU and General Ward	40.0% (*n* = 24)	-	-	-
27.	Chang, Rockman [40] USA	Retrospective 188	General ward	-	30.9% (*n* = 58)	-	-
28.	Chaudhary, Padrnos [41] USA	Retrospective 102	General ward	1.0% (*n* = 1)	2.9% (*n* = 3)	1.0% (*n* = 1)	2.0% (*n* = 2)
29.	Fujiwara, Nakajima [42] Japan (Asia)	Retrospective 628	ICU and General Ward	1.8% (*n* = 11)	2.1% (*n* = 13)	-	-
30.	Helms, Tacquard [43] French (Europe)	Prospective 150	ICU	16.7% (*n* = 25)	2.0% (*n* = 3)	0.6% (*n* = 1)	-
31.	Lodigiani, Iapichino [44] Italy (Europe)	Retrospective 388	ICU and General Ward	2.6% (*n* = 10)	1.3% (*n* = 5)	2.3% (*n* = 9)	1.0% (*n* = 4)
32.	Cueto-Robledo, Navarro-Vergara [45] Mexico (North USA)	Prospective 26	General ward	34.6% (*n* = 9)	3.8% (*n* = 1)	3.8% (*n* = 1)	-
33.	Fraissé, Logre [46] French (Europe)	Retrospective 92	ICU	20.1% (*n* = 19)	6.5% (*n* = 6)	2.2% (*n* = 2)	1.1% (*n* = 1)

Eleven articles recorded patients' discharge status in their studies [14–17, 25, 27, 29, 30, 34, 35, 40]. The number of discharged patients ranged from 12.0% ($n=22$) [14] to 79.1% ($n=22$) [34] (Table 2). Patients in the general ward exhibited a higher tendency to discharge (45.7% [16] to 77.2%) [30] compared to those in the ICU [14] to 60.5% [27] (Table 3).

Meanwhile, there were twelve articles [14–17, 22, 25, 27, 29, 30, 34, 35, 40] reported that 1.1% ($n=68$) [34] to 80.8% ($n=485$) [22] of their patients remained hospitalized with higher tendencies among those in the ICU compared to patients in the general ward [75.5% [14] vs. 39.1% [16] respectively] (Table 3).

Lastly, 21 studies [14–17, 22, 25, 27–36, 38–42] recorded patients' death status with incidence ranging from 4.8% ($n=30$) [42] to 63.1% ($n=125$) [28]. COVID-19 patients who were critically ill had a higher incidence of mortality [12% ($n=23$) to 63% ($n=125$]) than those in the general ward [35.6% ($n=248$]) (Table 3).

Incidence of mortality in COVID-19 patients associated with TE complications

Meanwhile, there were 16 studies that reported mortality associated with TE complications [16, 18, 23, 25, 27, 29–31, 33, 35, 36, 38–40, 44, 46]. The incidence of mortality in hospitalised COVID-19 patients due to TE

Table 3 Outcome for study population

Bil.	Study	No of samples	Study Setting	Discharged	Still Hospitalized	Death
1.	Klok, Kruip [14]	184	ICU	12.0% ($n=22$)	75.5% ($n=139$)	12.5% ($n=23$)
2.	Bozzani, Arici [27]	38	ICU	60.5% ($n=23$)	15.8% ($n=6$)	23.7% ($n=9$)
3.	Elboushi, Syed [28]	198	ICU	-	-	63.1% ($n=125$)
4.	Brandao, de Oliveira [32]	243	ICU	-	-	31.7% ($n=77$)
5.	Haksteen, Hilderink [33]	188	ICU	-	-	26.6% ($n=50$)
6.	Mohamud and Mukhtar [16]	46	General Ward	45.7% ($n=21$)	39.1% ($n=18$)	15.2% ($n=7$)
7.	Valle, Bonaffini [35]	114	General Ward	63.2% ($n=72$)	21.9% ($n=25$)	14.9% ($n=17$)
8.	Silva, Jorge [36]	300	General Ward	-	-	23% ($n=69$)
9.	Vivan, Rigatti [38]	697	General Ward	-	-	35.6% ($n=248$)
10.	Chang, Rockman [40]	183	General Ward	43.7% ($n=80$)	33.3% ($n=61$)	23.0% ($n=42$)
11.	Rali, O'Corragain [29]	147	General Ward	49.0% ($n=72$)	24.5% ($n=36$)	26.5% ($n=39$)
12.	Erben, Franco-Mesa [30]	915	General Ward	77.2% ($n=707$)	13.9% ($n=127$)	8.9% ($n=81$)
13.	Bruggemann, Spaetgens [39]	60	ICU and General Ward	-	-	28.3% ($n=17$)
14.	Filippi, Sartori [31]	267	ICU and General Ward	-	-	17.6% ($n=47$)
15.	Kaptein, Stals [17]	947	ICU and General Ward	76.2% ($n=722$)	8.6% ($n=81$)	15.2% ($n=144$)
16.	Martinot, Eyriey [22]	600	ICU and General Ward	-	80.8% ($n=485$)	19.2% ($n=115$)
17.	Arribalzaga, Martinez-Alfonzo [34]	5966	ICU and General Ward	79.1% ($n=4717$)	1.1% ($n=68$)	19.8% ($n=1181$)
18.	Tholin, Fiskvik [25]	550	ICU and General Ward	40.5% ($n=223$)	48.4% ($n=266$)	11.1% ($n=61$)
19.	Al-Samkari, Karp Leaf [15]	400	ICU and General Ward	55.7% ($n=223$)	37.0% ($n=148$)	7.3% ($n=29$)
20.	Chaudhary, Padrnos [41]	102	ICU and General Ward	-	-	8.8% ($n=9$)
21.	Fujiwara, Nakajima [42]	628	ICU and General Ward	-	-	4.8% ($n=30$)

complications ranges from 5.3% [25] to 48.6% [46]. The ICU setting reported the highest incidence, ranging from 23.6% [18] to 48.6% [46]. The general ward has reported a mortality incidence associated with TE complications as high as 42.5% [38] (Table 4).

Discussion

In this study, the incidence of TE complications and mortality associated with TE complications in hospitalized COVID-19 patients from European, American, African, and Asian populations were reviewed. The findings showed that hospitalised COVID-19 patients had a high tendency to develop TE complications, which could lead to increased mortality, especially in severely ill patients.

A wide range of TE complications can be seen especially PE (1.0-57%) [35, 41] and DVT (0.4-84.2%) [27, 34] due to large differences in populations across the studies. Although the number of VTE cases reported was relatively comparable with that in other studies, the limited number of patients tended to overestimate the episodes of VTE complications, as the overall cases were summarized in percentage. Hence, studies with small sample sizes tend to report a high incidence of VTE complications [20, 21, 27, 35, 39, 45]. Furthermore, differences in definitions in each study may account for the discrepancy in the incidence of TE complications. For example, a study conducted in the Netherlands [33] reported the incidence of general VTE complications instead of categorizing each VTE event, resulting in an elevated rate of VTE (43.1%, $n=81/188$).

Moreover, the methods used to diagnose TE complications in each study varied, which could lead to wide variability in the reported incidences. A study [15] found that attending clinicians could not confirm some presumed cases of VTE without clinical evidence consistent with VTE and strong clinical suspicion. This is due to the inability to perform the necessary tests secondary to the diagnostic limitations imposed by the COVID-19 infection.

Aside from that, the wide variation in the incidence of TE complications among hospitalized COVID-19 patients may be due to the absence of a diagnosis for asymptomatic patients, which limits the amount of data collected globally [48]. Moreover, the high number of patients admitted during the COVID-19 pandemic era led to a limited screening for TE complications throughout their hospitalization period. Moreover, two European studies [49, 50] reported that hospital acquired VTE still occurred within 42 days post-discharge and may indicate that some VTE remains undetected, especially in asymptomatic patients.

Similarly, a Dutch study observed no screening for TE complications during admission, unless the patient had a clinical suspicion [17]. As a result, some TE complications remain undiagnosed. These observations were supported by autopsy findings, in which nearly half of the patients ($n=11/26$) had TE complications, although it was not suspected prior to post-mortem [51]. Therefore, we may underestimate the actual number of TE complications among hospitalized COVID-19 patients.

It was observed that COVID-19 patients in general populations were more likely to develop VTE as compared to ATE complications [14–19, 21–46, 52]. This is explained by the characteristics of the vein, with low pressure owing to the vessel structure and low velocity owing to blood movement against gravity [53]. Most hospitalized COVID-19 patients were either bedridden or isolated in their designated wards. Therefore, restricting their movement and slowing blood flow in veins results in low oxygen tension in the venous wall and a cellular response to initiate inflammation-like TE complications [54, 55].

This review included seven studies, where the patient outcomes varied depending on the study settings: ICU or general ward: ICU or general ward [14, 16, 27, 29, 30, 35, 40]. Patients in the general ward had a higher tendency to be discharged [45.7% [16] to 77.2% [30] than those in the ICU [12.0% [14] to 60.5% [27]. In addition, the incidence of COVID-19 patients who remained hospitalized was also higher among patients in the ICU [15.8% [27] to 75.5% [14] than among those in the general ward [13.9% [30] to 39.1% [16]. This finding is consistent with that of a previous study [9] which showed a higher risk of VTE in the critically ill population due to pre-existing comorbidities and risk factors such as active cancer and a previous history of venous thromboembolism compared to those in the general ward.

ICU patients were more likely to experience all-cause mortality [63.1% [28] vs. 35.6%] [38]. Similarly, ICU patients also had the highest incidence of TE complication-related mortality compared to the other two wards: the general ward and the combination ward [48.6% [46] vs. 42.5% [38] and 37.5% [39]]. The difference in mortality rates in these studies may be related to the patients' disease prognosis. Critically ill patients are more likely to become hypercoagulable because they can't move, use mechanical ventilation, or have nutritional deficiencies compared to patients in the medical ward. This exposed them to a higher risk of mortality [56]. Our findings suggest that regardless of the condition of the patients during hospitalization, TE complications in hospitalized COVID-19 patients could lead to poor disease prognosis, thereby increasing patient morbidity and mortality.

By recognizing the incidence of TE complications and mortality in the articles, we gain insight into the burden of TE complications among COVID-19 patients and observe their management across different studies. Most

Table 4 Incidence of mortality in COVID-19 patients

Bil.	Study	No of samples	Study Setting	Mortality in hospitalized COVID-19 Patients (Number of mortality cases)	Mortality in hospitalized COVID-19 patients due to TE Complication (Number of mortality from TE / all TE cases)
1.	Klok, Kruip [14]	184	ICU	12.5% (*n* = 23)	-
2.	Gonzalez-Fajardo, Ansuategui [18]	261	ICU	-	23.6% (*n* = 25/106)
3.	Bozzani, Arici [27]	38	ICU	23.7% (*n* = 9)	28.1% (*n* = 9/32)
4.	Elboushi, Syed [28]	198	ICU	63.1% (*n* = 125)	-
5.	Brandao, de Oliveira [32]	243	ICU	31.7% (*n* = 77)	-
6.	Haksteen, Hilderink [33]	188	ICU	26.6% (*n* = 50)	25.9% (*n* = 21/81)
7.	Fraissé, Logre [46]	92	ICU	41.3% (*n* = 38)	48.6% (*n* = 18/37)
8.	Mohamud and Mukhtar [16]	46	General ward	15.2% (*n* = 7)	31.6% (*n* = 6/19)
9.	Rali, O'Corragain [29]	147	General ward	26.5% (*n* = 39)	40.0% (*n* = 12/30)
10.	Erben, Franco-Mesa [30]	915	General ward	8.9% (*n* = 81)	15.9% (*n* = 13/82)
11.	Valle, Bonaffini [35]	114	General ward	14.9% (*n* = 17)	16.9% (*n* = 11/65)
12.	Silva, Jorge [36]	300	General ward	23.0% (*n* = 69)	26.1% (*n* = 12/46)
13.	Vivan, Rigatti [38]	697	General ward	35.6% (*n* = 248)	42.5% (*n* = 96/226)
14.	Chang, Rockman [40]	183	General ward	23.0% (*n* = 42)	19.0% (*n* = 11/58)
15.	Chaudhary, Padrnos [41]	102	General ward	8.8% (*n* = 9)	-
16.	Al-Samkari, Karp Leaf [15]	400	ICU and General Ward	7.3% (*n* = 29)	-
17.	Martinot, Eyriey [22]	600	ICU and General Ward	19.2% (*n* = 115)	-
18.	Munoz-Rivas, Abad-Motos [23]	1127	ICU and General Ward	-	15.9% (*n* = 11/69)
19.	Tholin, Fiskvik [25]	550	ICU and General Ward	11.1% (*n* = 61)	5.3% (*n* = 2/38)
20.	Arribalzaga, Martinez-Alfonzo [34]	5966	ICU and General Ward	19.8% (*n* = 1181)	-
21.	Bruggemann, Spaetgens [39]	60	ICU and General Ward	28.3% (*n* = 17)	37.5% (*n* = 9/24)
22.	Filippi, Sartori [31]	267	ICU and General Ward	17.6% (*n* = 47)	24.0% (*n* = 12/50)
23.	Fujiwara, Nakajima [42]	628	ICU and General Ward	4.8% (*n* = 30)	-
24.	Lodigiani, Iapichino [44]	388	ICU and General Ward	-	25.0% (*n* = 7/28)
25.	Kaptein, Stals [17]	947	ICU and General Ward	15.2% (*n* = 144)	-

studies [14, 15, 17, 18, 23, 26, 28–39, 41, 42, 44, 46, 57] reported administering thromboprophylaxis to their hospitalized COVID-19 patients. Upon recognition of TE complications, patients received a therapeutic dose of anticoagulant in the absence of prophylactic management [16, 34, 40, 58]. Due to the unknown extent of COVID-19 infection on TE complications at the time, most practitioners had to outweigh the risk and benefit of introducing thromboprophylaxis strategies, either anticoagulants or antiplatelet agents, to hospitalized COVID-19 patients [59] (Table 5).

The incidence of every reported outcome suggests that the management of TE complications used in all studies may be the cause of potential discrepancies. The management of thromboprophylaxis and therapeutic strategies involving antiplatelet or anticoagulant differed according to the study protocol and local guidelines. A postmortem examination done in seven COVID-19 patients found platelet-rich thrombi in several organs, such as the pulmonary, hepatic, renal, and cardiac microvasculature [60]. From this finding, we can postulate that the beneficial effect of antiplatelets such as acetylsalicylic acid (ASA) had the advantage of preventing microthrombi in COVID-19 patients [61]. Furthermore, several studies found ASA has a pleiotropic effect of disturbing virus replication on the endothelium cell, which may target the development of endotheliitis in COVID-19 patients [62, 63]. In situations involving endothelial damage whereby the platelets stick to the injured site, causing thrombosis, antiplatelets such as ASA will be relevant in prophylactic treatment in preventing platelets from clumping together, hence causing TE complications [64]. However, ASA is also known for its bleeding complication, hence making it a contraindication for patients with an existing risk of bleeding.

On the other hand, anticoagulants such as heparin, low molecular-weight heparin (LMWH), or unfractionated heparin (UFH) have anti-inflammatory properties due to their ability to inhibit the formation of thrombin and reduce inflammatory responses [65]. Moreover, its antiviral potency explains the prevention of COVID-19 viral entry by acting on the angiotensin-converting enzyme 2 receptor and interacting with COVID-19 spike glycoprotein [61]. Despite its advantages of being pluripotent in nature, patients may develop heparin resistance and may need close monitoring of some parameters such as antithrombin activity, platelet count, factor VII, and fibrinogen level [63].

Several studies compared the outcomes of COVID-19 infection severity or mortality in patients receiving anticoagulant prophylactic dose versus anticoagulant therapeutic dose in hospitalized COVID-19 patients [66–71]. Most of the intervention studies found no significant outcomes in both prophylactic and therapeutic groups. An intervention study performed in Brazil compared the prophylactic regime (enoxaparin or UFH) and therapeutic dose (rivaroxaban: stable patients and enoxaparin or UFH: unstable patients). The result of this study found no significant beneficial effect of prophylactic over therapeutic regimes in terms of mortality or length of hospital stay. Instead, there was a significant increase in bleeding events in the therapeutic cohort (8% vs. 2%, $p=0.0010$) [69]. The result was further supported by another intervention study conducted in critically ill hospitalized COVID-19 patients, which found the therapeutic dose of heparin showed no significant superiority in reducing mortality compared to the prophylactic group (OR 0.84; 95 CI: 0.64–1.11) [70]. Another multicentre randomized trial involving 28 hospitals in 6 countries among moderately ill COVID-19 patients with elevated d-dimer compared the standard prophylactic heparin dose with the standard therapeutic dose [66]. This study found that the therapeutic group did not show any significant association with a reduction of the primary composite of death, mechanical ventilation, or ICU admission compared with prophylactic heparin (OR: 0.69, 95% CI: 0.43–1.10, $P=0.12$).

In contrast, a multicenter randomized clinical trial done by Spyropoulos, Goldin [67] found that within non-critically ill hospitalized COVID-19 patients, the therapeutic dose (enoxaparin) was associated with a reduction in TE complications (RR, 0.37; 95% CI, 0.21–0.66; $P<0.001$) and a reduction in mortality at 28 days of hospitalization (relative risk (RR), 0.68; 95% CI, 0.49–0.96; $p=0.03$). However, the result was different in critically ill COVID-19 patients in the ICU as the primary outcome, which showed no significant difference in TE complications in both groups (RR 0.92; 95% CI, 0.62–1.39; $p=0.71$). Hence, we can presume that the condition of the patient played an important factor in determining which group had a superior beneficial effect.

In addition, the wide range of mortality (12.5-63.1%) [14, 28] in critically ill COVID-19 patients may be due to variations in heparin administration and thromboprophylaxis management. According to a study [72], the incidence of mortality was high in COVID-19 patients with elevated D-dimer levels who did not receive any thromboprophylaxis treatment. Researchers further supported this results by finding that both therapeutic and prophylactic anticoagulant regimens were associated with a reduction in in-hospital mortality compared to patients without anticoagulants [51].

In addition to the benefit of prophylaxis management in hospitalized COVID-19 patients, researchers in every study need to consider the risk of bleeding in their study populations. This is crucial, as every patient started on an anticoagulant may encounter the risk of hemorrhage. A study conducted by [51] found that some patients

Table 5 Comparison in prophylaxis strategy

No.	First Author Location	Preventive and Manamegent Strategy		No anticoagulant
		Prophylaxis	Therapeutic	
1	Klok, Kruip [10]	All patients received at least standard doses thromboprophylaxis.	-	-
2	Al-Samkari, Karp Leaf [28]	All patients received standard dose thromboprophylaxis.	-	-
3	Mohamud and Mukhtar [39]	-	Only patients with thromboembolic event administered with therapeutic anticoagulant.	Most patients did not receive any prophylaxis.
4	Kaptein, Stals [11]	All patients received standard dose thromboprophylaxis	-	-
5	Gonzalez-Fajardo, Ansuategui [12]	33 patients (31.13%) were treated with thromboprophylaxis. (Low Molecular Weight Heparin)	-	Most patients did not receive any prophylaxis.
6	Munoz-Rivas, Abad-Motos [16]	All patients received standard dose thromboprophylaxis.	Only patients with confirmed TE complications given therapeutic dose.	-
7	Tholin, Fiskvik [17]	Most patients received thromboprophylaxis (61%).	-	-
8	Martínez Chamorro, Revilla Ostolaza [18]	All patients received prophylaxis. (Enoxaparin)	-	-
9	Elboushi, Syed [41]	All patients received prophylaxis. (Low Molecular Weight Heparin)	-	-
10	Rali, O'Corragain [29]	All patients received dose of thromboprophylaxis.	-	-
11	Erben, Franco-Mesa [30]	All patients received standard dose thromboprophylaxis. (Heparin)	-	-
12	Filippi, Sartori [31] USA	Most patients given thromboprophylaxis. (Low Molecular Weight Heparin)	-	-
13	Brandao, de Oliveira [32]	Most patients (72%) given thromboprophylaxis. (Low Molecular Weight Heparin)	-	-
14	Haksteen, Hilderink [20]	All patients received standard dose thromboprophylaxis. (Nadroparin)	-	-
15	Arribalzaga, Martinez-Alfonzo [21]	Most patients (68.3%) received standard prophylactic dose. (Low Molecular Weight Heparin)	Intermediate and therapeutic doses of LMWH were used more in ICU patients (18%) than in ward patients (12.6%).	-
16	Valle, Bonaffini [22]	91 patients received standard prophylactic dose.	-	-
17	Silva, Jorge [27]	29 patients received standard prophylactic dose.	-	-
18	Whyte, Kelly [42]	All patients given thromboprophylaxis in the absence of contraindication	-	-
19	Bruggemann, Spaetgens [23]	Most patients (55%) received standard prophylactic dose.	-	-
20	Chang, Rockman [34]	-	Most patients (62.2%) received therapeutic dose.	-
21	Chaudhary, Padrnos [35]	Most patients (80.4%) received standard prophylactic dose.	-	-
22	Fujiwara, Nakajima [38]	Only 10% received standard prophylactic dose. Mostly in ICU ($n=20/35$ patients)	-	-
23	Lodigiani, Iapichino [25]	Thromboprophylaxis was used in 100% of ICU patients and 75% of those on the general ward.	-	-
24	Vivan, Rigatti [38]	68% of patients were receiving prophylactic or therapeutic doses. (Heparin)		-
25	Fraissé, Logre [26]	All patients received usual (prophylactic) or full-dose (therapeutic) anticoagulation according to their risk factors for thrombosis		-

experienced bleeding events after the initiation of anticoagulant treatment. Patients who started on therapeutic doses experienced a higher rate of bleeding compared to those who did not receive any anticoagulants.

Although the episodes of bleeding complications were comparable in both the prophylaxis and therapeutic-dose groups [71], there was a difference in intensity depending on the type of anticoagulant used. For example, patients who were given a single preventative agent had higher bleeding rates when taking unfractionated heparin (UFH) than when taking low molecular weight heparin (LMWH). On the other hand, patients who were given therapeutic agents had higher bleeding rates when taking LMWH than when taking direct oral anticoagulants (DOACs) [51].

Finally, the limitations of this study should be considered. Although there was no duplication in the selected articles, there may be unintended bias due to the absence of registration in the PROPERO system.

Conclusions

Overall, there was a wide range of incidences of both VTE complications and ATE complications among hospitalized COVID-19 patients (VTE: 0.4-84% and ATE: 0.5-15.2%). Similarly, a wide variation in the incidence between all-cause mortality in COVID-19 and the incidence of mortality associated with TE complications was seen in hospitalized COVID-19 patients (all-cause mortality:4.8-63.1% and mortality associated with TE complications:5.3-48.6%). These discrepancies may be the result of different definitions, diagnostic methods, and prophylaxis management across all the included studies. Multinational, multicenter data included in this review summarized the common occurrence of TE complications and associated mortality in COVID-19 patients. Therefore, every patient should undergo a thorough risk factor assessment for TE complications and allow individualized optimal thromboprophylaxis management to improve the patient's outcome.

Author contributions

Conceptualization, H.H.Z., I.A.H.Z., M.R.I., H.Y.O.; methodology, H.H.Z., L.C.M., I.A.H.Z., M.R.I., H.Y.O.; software, H.Y.O., H.H.Z., L.C.M.; validation, H.Y.O., H.H.Z., A.H., M.R.I., I.A.H.Z.; resources, I.A.H.Z., H.H.Z., H.Y.O.; writing—original draft preparation, H.Y.O., L.C.M., H.H.Z., I.A.H.Z.; writing—review and editing, H.H.Z., L.C.M., I.A.H.Z., M.R.I., H.Y.O.; visualization, H.Y.O., L.C.M., M.R.I.; supervision, H.H.Z.; project administration, M.R.I., I.A.H.Z., H.H.Z., H.Y.O.; All authors have read and agreed to the published version of the manuscript.

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