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Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 535–541

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

A systematic review of clinical and laboratory parameters associated with increased severity among COVID-19 patients

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ARTICLE INFO

Article history:
Received 31 October 2020
Received in revised form
5 February 2021
Accepted 12 February 2021

Keywords:
COVID-19
Systematic review
Clinical symptoms
Laboratory parameters

ABSTRACT

Background and aims: Corona virus disease 2019 (COVID-19) has been an extremely difficult pandemic to contain and it has affected more than 148 countries worldwide. The main aim of this systematic review is to provide a comprehensive summary of clinical and laboratory parameters that are associated with and indicative of increased severity among COVID-19 patients.
Material and methods: All the available data from high-quality research articles relevant to the epidemiology, demographics, trends in hospitalization and outcomes, clinical signs and symptoms, diagnostic methods and treatment methods of COVID-19 were retrieved and evaluated for inclusion.
Results: As per our review, the mean age of patients in the severe group was 59.3 years compared to 46.5 years in non severe group. COVID-19 was more severe among men than women. Clinical presentation was variable among different studies. and dyspnea was the factor indicating severe disease. Laboratory parameters associated with increased severity were lymphopenia <0.8 × 10^9/L, thrombocytopenia 100 × 10^9/L, leucocytosis TC > 11 × 10^9/L, procalcitonin >0.5 ng/mL, d dimer >2 mcg/mL, aspartate transaminase elevation >150U/L, LDH >250U/L.
Conclusion: This systematic review suggests that COVID-19 is a disease with varied clinical presentation and laboratory parameters. The commonest clinical symptoms were fever, cough and dyspnea. The laboratory parameters associated with severe disease were lymphopenia, elevated LDH, D dimer and Procalcitonin.

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1. Introduction

According to World health organization (WHO) Corona virus disease 2019 (COVID-19) has infected more than 2,628,527 individuals spread over 148 countries worldwide and has been responsible for more than 182,424 deaths as of April 23, 2020. It has been declared a global pandemicby the WHO on March 11, 2020.

Compared to severe acute respiratory syndrome (SARS) and Middle east respiratory syndrome (MERS), COVID-19 behaves differently. It has a more rapid transmission and longer incubation period both of which adds to the woe of disease containment...

The primary aim of this systematic review is to provide a comprehensive clinical summary of the available data relevant to the epidemiology, demographics, trends in hospitalization and outcomes, clinical signs and symptoms, diagnostic and treatment methods of COVID-19. A systematic and protocol-driven approach is required to contain this disease. The current study is a cohesive literature review on clinical symptoms as well as laboratory parameters associated with increased severity of COVID-19. **Objectives:**

Primary Outcome: The primary aim is to identify the risk factors associated with increased severity in COVID- 19 patients.

Secondary Outcome: The secondary outcome was to identify the co-morbidities associated with increased severity in COVID-19.

2. Methods

We performed this review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [1]. An Institutional Review Board approval was not necessary as this work involved systematic review and meta-analysis of

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https://doi.org/10.1016/j.dsx.2021.02.020
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previously published studies.

We searched the PubMed, the largest and Science Direct, for articles indexed up to March 2020. We updated our search on April 4, 2020. Our search strategy for the PubMed database was ("COVID-19 and clinical features associated with increased severity).

All the studies that included confirmed COVID-19 cases and studied factors affecting its severity were included in the analysis. The studies were either original article or case series on COVID-19 patients which were published or accepted (and in pre print form) from December 2019 to March 2020 in English literature.

3. Data extraction and analysis

The investigator (MA) performed the literature search and extracted the data with three other investigators (B P, W J and H N) from included studies. We resolved disagreements with a discussion and consensus. We extracted the following variables: author, date, age, gender, number of participates in severe and non-severe groups. We also included data on the prevalence of clinical symptoms such as fever, cough, fatigue, and dyspnoea and presence of co morbidities e.g: hypertension, diabetes, respiratory system disease, and cardiovascular diseases. The flow of the study selection is shown in Fig. 1 [2–18].

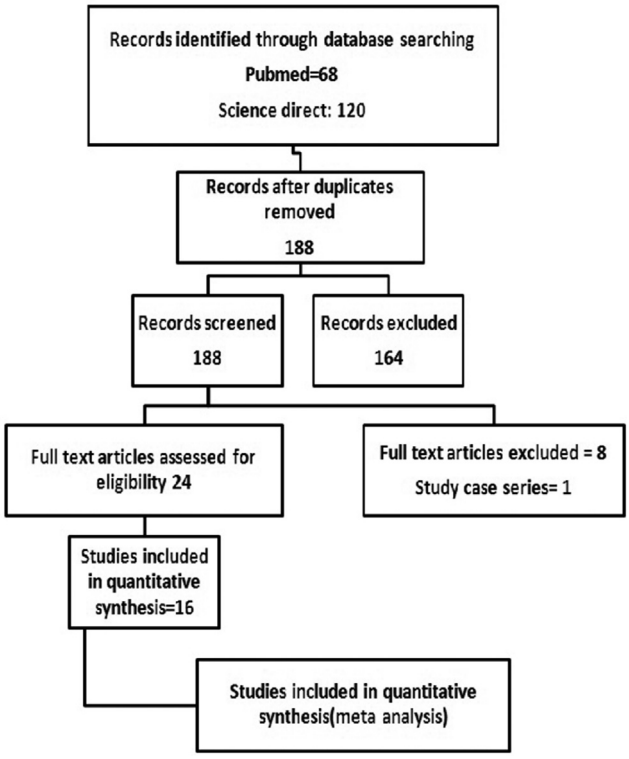

Fig. 1. showing flow diagram of number of studies screened and included in the meta analysis.

We have enlisted the included studies and their type in Table 1.

We have included all the studies on patients with confirmed diagnosis of SARS Corona virus −2 by RT PCR and published in English literature up to April 4, 2020. Details of clinical features like baseline demographics, symptomatology, presence of co morbidities, and laboratory investigations and clinical management were gathered. Patients with more severe disease were compared with those with non severe disease.

4. Inclusion criteria

We included all the studies on COVID-19 patients published in English language in indexed journals.

5. Exclusion criteria

Studies which did not include data on severity of COVID-19 were excluded.

6. Study results

Baseline demographics:

7. Age distribution among severe and non sever patients

The study by W Guan J [6] et al., reported COVID-19 affected patient's mean age to be 45 years (35–58). The mean age of patients with severe COVID-19 disease was 52 years (40–65) in comparison to mean age of 45 years in those with non severe disease. The age distribution of COVID- 19 patients in study by Dawei Wang et al. [9] was 56 years (42–68), 66 years (57–78), and 51 years (37–62) years respectively for overall group, severe and non severe patients respectively. Jin-jin Zhang et al. [12] described mean age of 57 years (25–87) in entire cohort, while, it was 51.5 years (26–78) and 62 years (25–87) in non severe and severe group respectively. According to Huang et al. [5] and Yu Shi et al. [15], SARS-CoV-2/COVID-19 seems to have a predilection for the elderly male population. According to the study published by Fei Zhou et al. [16], the mean age of non survivors was 69 (63–76) while among survivors it was 52(45–58) years. Wei Liu et al. [17] showed that mean age of population which had progressive disease was 66 years while it was 37 years for those who had stable disease. As per the study by Xiaobo Yang et al. [18], the survivors mean age was 51.9 year compared to 64.6 years among non survivors. These findings are summarized in Fig. 2.

8. Gender

In general, COVID-19 was more severe in males compared to

Table: 1
Table showing studies included in systematic review.

Study name	N	Study type	Comparison groups details
Huang et al. [5]	41	Prospective	ICU with Non ICU
Guan et al. [6]	1096	Retrospective	Non severe with severe
Wei Guan et al. [9]	138	Retrospective	ICU with Non ICU
Zhang Xiaolie al [10].	645	Prospective	Normal chest x ray with abnormal chest x ray
Zhang Jin et al. [12]	140	Retrospective	Non severe with severe
Shi Yu et al. [15]	487	Retrospective	Mild with severe
Zhou et al. [16]	191	Retrospective	Non Survivor with survivors
Liu Wei et al. [17]	78	Prospective	Stable with progression
Xiabo Yang et al. [18]	52	Retrospective	Non Survivor with survivors

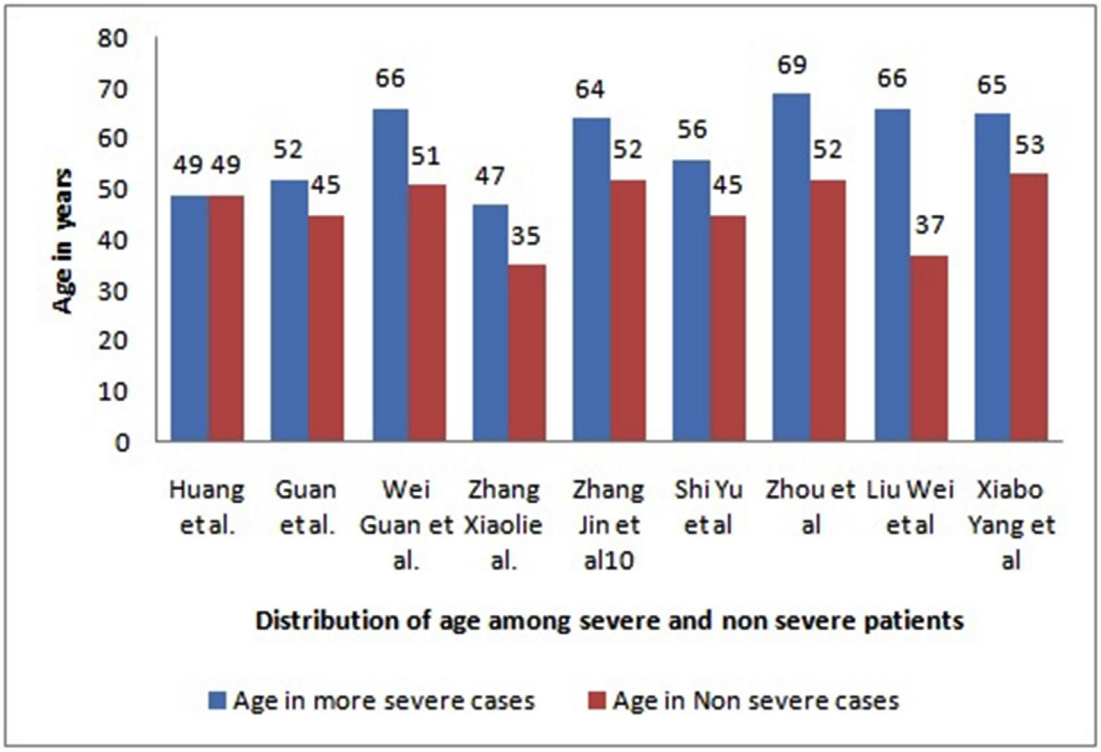

Fig. 2. showing distribution of age among severe and non severe COVID-19 patients.

female population. In a study reported by Xiaobo Yang et al. only 46% patients were women [18]. These results for multiple studies are summarized in Fig. 3.

9. Clinical signs/symptoms

Fever was the most common symptom followed by dyspnoea and productive cough. W Guan Z et al. [6] studied 1096 patients with COVID-19 in China. Clinical symptoms noted were fever (3.51%), cough (67.8%), expectoration (33.8), dyspnoea (18.7), muscle ache (14.9) and sore throat (13.9). In severe cases, dyspnea was present in 37.6% of the patients.

Huang et al. [5] analyzed 41 patients of COVID-19, of which 40 (98%) had fever and 31 (76%) had cough. Of the 40 patients with fever, 13 were in managed in intensive care units and 27 were in treated in the wards. Other symptoms in COVID-19 confirmed cases were expectoration (39%), dyspnoea (40%) muscle ache (43%) fatigue (16%), headache (10%), gastrointestinal discomfort (2%), shortness of breath (SOB) (55%) and [5]. Huang et al. noted that the average time from onset of symptoms to hospitalization was 8 days.

Dawei Wang et al. [9] in a study of 138 patients reported that the median time from starting of symptom to hospital admission was about 7 days (4–8) and time from hospital admission to ARDS was 8 days (6–12). They found 136 (98.5%) had fever, 36 (26%) required ICU. Fever was the most common symptom, followed by cough 69.6%, expectoration 26.8%, dyspnoea 31.2%, sore throat in 17.4% and muscle ache in 34.8% of patients. Eighty two (55%) patients recuperated while 68 (45%) patients succumbed to the disease.

Jin-jin Zhang et al. [12] studied 140 patients and commonest clinical symptoms were fever (91.7%), cough (75%) and dyspnoea (36.7%). Other clinical symptoms and their relationship with severity are shown in Fig. 4. Fei Zhou et al. [14] analyzed 191 patients and fever (94%), cough (79%) expectoration (23%) and muscle ache (15%) were commonest symptoms in their study too. Time from first symptom to hospital admission was 11 days (8–14). Time from hospital admission to death/discharge was 21 days (17–25). Forty two (21.98%) patients died of the disease. Yang et al. [18] analyzed 52 cases of RT-PCR confirmed COVID-19 in Wuhan and commonest symptoms found were fever (98%), cough (77%), and SOB (63.5%) [18]. However, a few of their patients had atypical symptoms like nausea, vomiting (4%) and.

The clinical signs and symptoms from different studies and their occurrence as per severity are summarized in Table 2.

10. Laboratory parameters

Lymphopenia was common among all patients irrespective of the severity status. Leucocytosis was common in the severe group as compared to the non severe group. Thrombocytopenia was also more commonly seen in the severely affected group except in the report by Hauang et al. [5] Elevation of procalcitonin and Serum LDH also showed a similar trend with higher incidence in the severely affected patients. Studies by Huang et al. [5] and Zhou et al. [16] showed variable response in elevation of Ferritin between severe and non severe group. Majority of the studies showed a larger percentage of severely ill patients had raised d-dimer levels. A larger percentage of the severely affected patients across all studies had raised transaminases.

Bilateral pneumonia was seen among the study population irrespective of the severity of the disease. But it was not as common among the non severe patient in the study by W.Guan et al. [8]. The detail of laboratory parameters and their relation with severity is shown in Table 3.

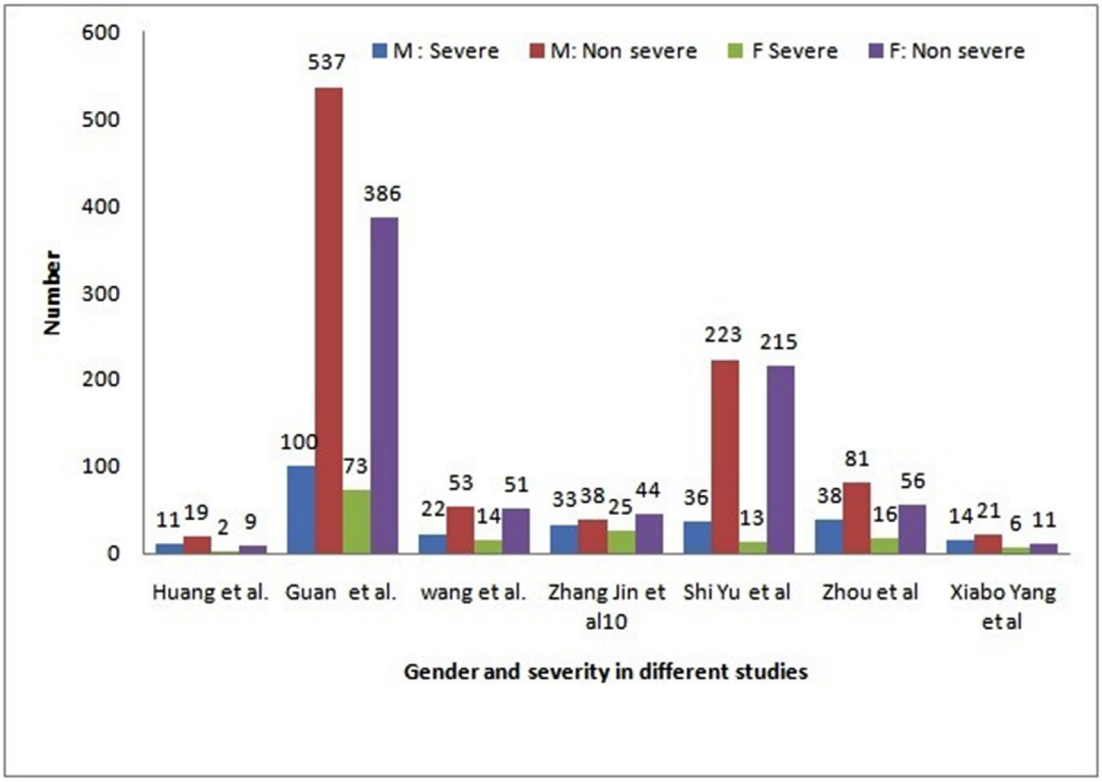

Fig. 3. showing distribution of gender among severe and non severe COVID-19 patients.

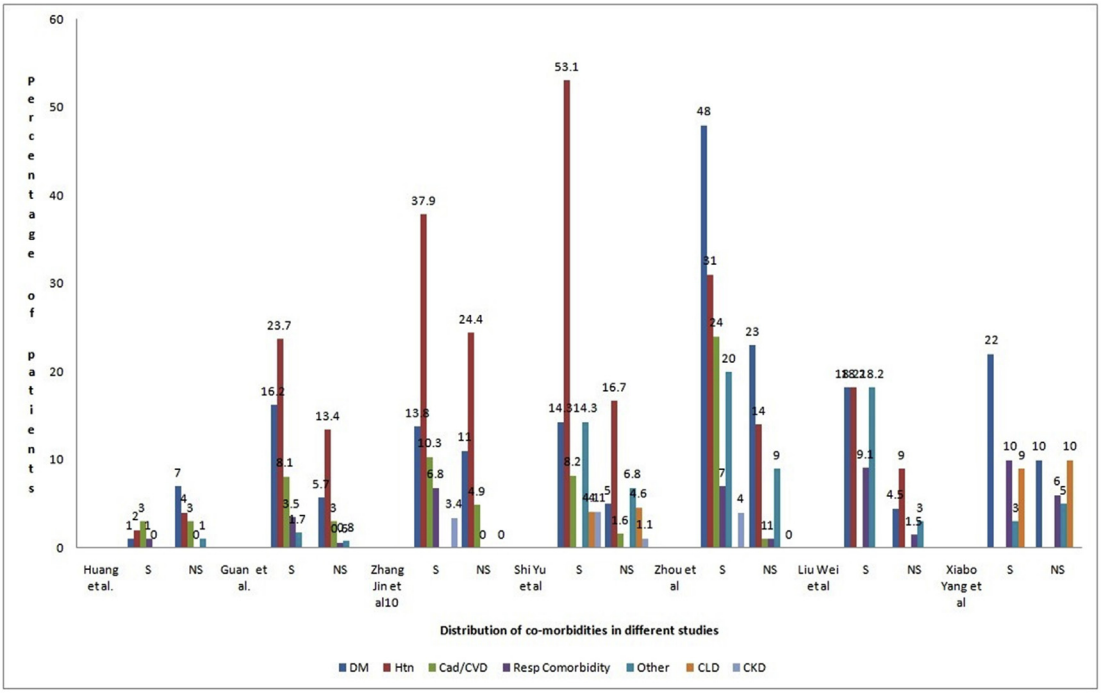

Fig. 4. showing co morbidities in severe and non severe COVID-19 patients.

11. Co morbidity and severity of COVID-19

Patients affected with COVID-19 were found to have multiple co-morbidities. Most studies reported higher morbidity and mortality with COVID-19 among patients with co-morbid conditions. Hypertension and diabetes mellitus was the commonest of comorbidities. Other common co-existent diseases included malignancies, respiratory disorders, chronic kidney disease and chronic liver disease. As shown in Fig. 3, underlying hypertension, cardiovascular disease and respiratory system disease were common co morbidities associated with severe disease.

Table: 2
Clinical symptoms in Severe (S) and non severe (NS) patients in different studies.

Study name	Huang et al. [5]			Guan et al. [6]			Dawei Wang et al. [9]			Zhang Xiaolie al [10].			Zhou et al. [16]			Xiabo Yang et al. [18]		
	Total	S(%)	NS(%)	Total	S(%)	NS(%)	Total	S(%)	NS(%)	Total	S(%)	NS(%)	Total	S(%)	NS(%)	Total	S(%)	NS (%)
Fever	40	13 (33)	27 (68)	38	8 (21)	30 (79)	136	36 (26)	100 (74)	110	51 (46)	59 (54)	180	51 (28)	129 (72)	51	31 (61)	20 (39)
Cough	21	11 (35)	20 (64)	47	122 (16)	623 (84)	96	29 (30)	67 (70)	90	45 (50)	45 (50)	42	31 (22)	112 (79)	40	25 (63)	15 (37)
Expectoration	11	5 (45)	6 54.5)	370	61 (16)	309 (84)	37	8 (21)	29 (78)	NA	NA	NA	44	14 (32)	30 (68)	NA	NA	NA
Dyspnea	22	12 (55)	10 (45)	205	65 (32)	140 (68)	43	23 (53)	20 (47)	44	24 (55)	20 (45)	NA	NA	NA	33	21 (63)	12 (37)
Sore throat	NA	NA	NA	153	23 (15)	130 (85)	24	12 (50)	12 (50)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Diarrhoea	0	0	1 (100)	42	10 (24)	32 (76)	14	4 (29)	10 (71)	18	9 (50)	9 (50)	9	2 (22)	7 (78)	NA	NA	NA
Nausea/vomiting	NA	NA	NA	56	12 (22)	43 (78)	5	3 (60)	2 (40)	24	5 (21)	19 (79)	7	3 (43)	4 (57)	2	1 (50)	1 (50)
Muscle ache	18	7 (39)	11 (61)	38	30 (18)	134 (82)	48	36 (75)	12 (25)	NA	NA	NA	29	8 (28)	21 (72)	6	4 (67)	2 (33)
Hemoptysis	2	1 (50)	1 (50)	10	4 (40)	6 (60)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

*S= Severe, #NS= Non severe, NA = not available.

Table 3
Laboratory parameters among severe and non severe patients.

Laboratory parameters ↓	c.Huang et al. [5] %		W Guan et al. [6] %		Jin-jin Zhang et al. [12] %		Fei Zhou et al. [16] %		Average %	
Disease severity →	NS	S	NS	S	NS	S	NS	S	NS	S
Leucocytosis(>11 × 10^9 cells per liter)	19	54	5	11	5	23	11	46	10	34
Lymphopenia(<0.8 × 10^9 cells per liter)	54	85	84	80	71	82	26	76	59	81
Thrombocytopenia(10^3 × 10^9 cells per liter)	4	8	32	58	NA	NA	1	20	12	29
Procalcitonin (>0.5 ng/mL)	0	23	4	14	24	50	1	25	7	28
CRP[1] increased(>150 µg/mL)	NA	NA	56	82	89	96	NA	NA	73	89
AST[2] (>150 units/Liter)	25	62	18	39	NA	NA	24	48	22	50
LDH[3] (>250 units/Liter)	63	92	37	58	NA	NA	54	98	51	83
Serum Ferritin (>200 ng/**mL)**	NA	NA	NA	NA	NA	NA	71	96	71	96
D dimer (>2 mcg/mL)	NA	NA	43	60	28	61	24	81	32	67
Cardiac Troponin I (>0.5 ng/mL)	NA	NA	NA	NA	NA	NA	1	46	1	46
Bilateral pneumonia	96	100	30	58	87	93	72	83	71	84

*S= Severe, #NS= Non severe, NA = not available.
1 = CRP: C reactive protein,2 AST = aspartate aminotransferase, 3 LDH **Lactate dehydrogenase**.

12. Need of ICU care, ventilator support among COVID-19

COVID 19 has become notorious for its respiratory system involvement in form of pneumonia and the subsequent requirement of ventilation support (Fig. 5).

W.Guan et al. [8] observed that 32.4% of severely ill patients required non invasive ventilation (NIV), 14.5% required invasive mechanical ventilation and 2.9% of the severely ill patients needed extracorporeal membrane oxygenation (ECMO). It is notable that none of the patients in the non severe group required any form of ventilatory support. The study by D.Wang et al. [9] and Zhang et al. [10] noted 10.9% and 12.32% of the severe patients were supported with NIV & invasive mechanical ventilation.

F.Zhou et al. [16] and Yang et al. [18] compared the data between survivors and non survivors of COVID-19. NIV and invasive mechanical ventilation were needed in 1% among the survivors. Among the non survivors 44%, 57% and 6% were supported with NIV, invasive mechanical ventilation or ECMO respectively. Yang et al. [18] recorded 10% of the survivors and 12.5% of the non survivors were provided prone positioning.

13. Discussion

COVID-19 has taken the entire world in its grip. As of April 23, 2020 more than 26,28,527 confirmed COVID 19 cases and 1,82,424 deaths have been reported worldwide [19]. A cluster of 41 cases of pneumonia who gave history of visit to local wild animal market within 30 days of infection was reported from Wuhan, Hubei province, China [20]. It was first identified and announced as a new corona virus (2019 nCoV) by a scientific team of Chinese Academy of Engineering [21]. COVID-19 has become a significant clinical threat to the general population and health care workers worldwide.[2,22] Unfortunately, knowledge about the novel virus is limited. Hence, the public needs to be educated to garner information from reliable sources such as the world health organization (WHO) [2]. A pandemic like COVID-19 exerts severe stress on every aspect of the society, and poses serious threat to international health and the economy. [2.3.22].

This systematic review aimed to elucidate the risk factors associated with increased severity of COVID-19, so that the countries that are still in the early phase of transmission can use the data and apply the information for better management of their patients and resources.

The current systematic review can also be used to develop severity scoring for COVID-19.

Final analysis mainly included 8 studies which described two groups in COVID-19, severe and non severe group. We noted that the mean age of severe group was 59.3 years compared to 46.5 years in non severe group. Sufficient studies have endorsed the same [4–18.] Our review also confirmed that men were affected more and had more severe disease compared to women.

We could not find any association between various clinical symptoms and their association with increased severity. As shown in Table 3, we could not find any particular symptom which could be more likely to represent more severe disease except dyspnoea which was consistently more common in severe group in all the studies [5–18]. The studies included in present review did not show any incidence of loss of smell and taste as one of the symptom, which recently has come across from many individual case series [19].

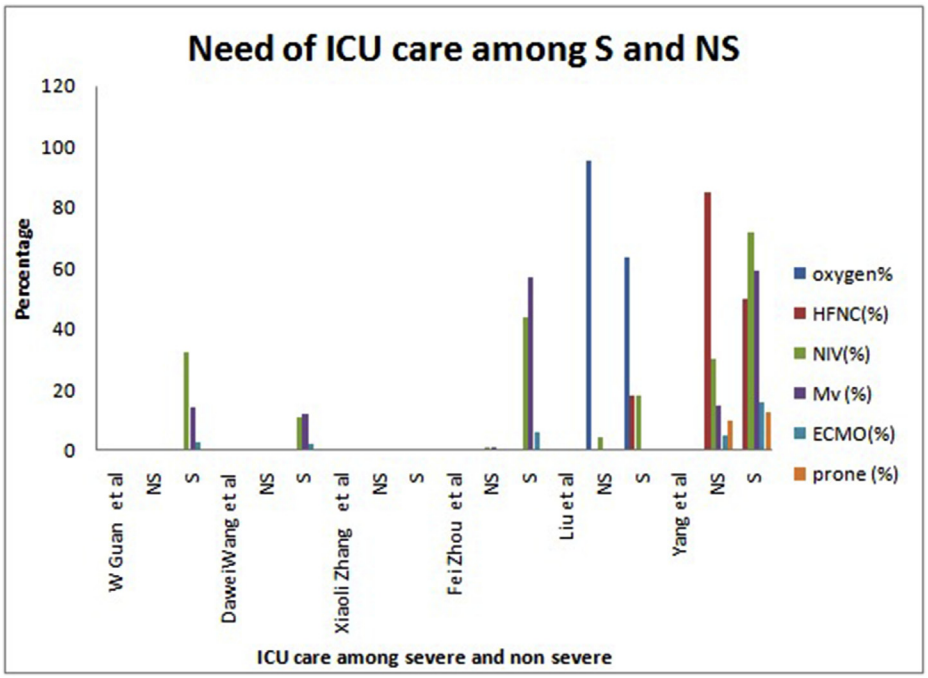

Fig. 5. showing need of ICU care among severe and non severe COVID-19 patients.

Laboratory parameters associated with more severe disease were lymphopenia <0.8 × 109/μL, thrombocytopenia <100 × 10^9/L, leucocytosis TC > 11 × 10^9/L procalcitonin >0.5, d dimer > 2 ng/mL, aspartate transaminase (AST) elevation > 150 units/L), LDH > 250U/L. There were very few studies which showed elevated ferritin and trop T. Elevated Ferritin, LDH, CRP, AST, d dimer can be attributed to cytokine storm which has been reported in COVID-19 patients [23].

Our review also found that severe COVID-19 cases occurred mostly in people with co-morbid conditions like hypertension, cancer and diabetes. Many of them developed various post COVID-19 complications e.g: coagulation activation, cellular immune deficiency, hepatic and kidney injury, secondary bacterial infection and myocardial injury. It has been understood that lymphopenia and sustained inflammation seen in patients with severe disease and death are most likely secondary to antibody-dependent enhancement (ADE) of COVID-19 due to previous exposure to other corona viruses [23,24]. A similar pattern was also seen in patients who had SARS epidemic in 2003 [25].

We found that patients requiring any form of ventilation generally belonged to the severe group. The studies included did not show sub group analysis and thus we could not confirm whether mechanical ventilation improved the survival. ARDS caused by viral pneumonia and role of mechanical ventilation has been published by many studies with similar results [25–27]. In general, the ARDS in viral pneumonia occurs in more severe patients [25–27] So, the survival rate among the patients requiring mechanical ventilation was lower [25,28]. Further, review is needed to find out the survival rate among the ventilated patients and factors affecting the survival so that judicious use of ventilator can be done in resource limited setting.

14. Limitations

The COVID-19 is rapidly evolving clinical condition and the data and available information changes every day. The studies included had heterogeneous distribution of population, and only two of them actually studied comparison among survivors and non survivors, and 4 of them addressed the issue of severe and non severe disease.

15. Conclusion

The present systematic review concludes that COVID-19 is lethal disease with varied clinical presentation and laboratory abnormalities. The commonest clinical symptoms were fever, cough and dyspnea. The laboratory parameters associated with severe disease were lymphopenia, elevated LDH, D dimer and procalcitonin >0.5 ng/mL. It is necessary for health care workers to identify those patients early, who are likely to have severe form of COVID-19 and take proactive steps to reduce morbidity and mortality, until effective therapeutics and vaccines are made discovered.

Declaration of competing interest

There is no conflict of interest.

Acknowledgement

The authors offer their gratitude to Dr Hisham Moosan, MD (Community Medicine), Department of Community Medicine, DM Wayanad Institute of Medical Sciences, for his guidance in initiating the project.

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