 doi:10.20944/preprints202211.0079.v1

Common Prognostic Biomarkers and outcomes in patients with COVID-19 infection

**Mashael Abujabal [1], **Mohamed A Shalaby[1], Layla Abdullah [1], Amr S Albanna[2] , Mohamed Elzoghby [3], Sidharth K. Sethi [4] , Mohamad-Hani Temsah [5], Fadi Aljamaan [6] , Khalid A Alhasan[5] and Jameela A Kari [*1]

1. Pediatric Nephrology Center of Excellence, King Abdulaziz University Hospital. Department of Pediatrics, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia; ameshoa@hotmail.com, dr.m.a.shalaby@gmail.com, layla.lab99@gmail.com, jkari@kau.edu.sa
2. King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Kingdom of Saudi Arabia; amralbanna@gmail.com
3. Pediatrics Department, PCICU, King Abdulaziz University hospital
4. Kidney and Renal Transplant Institute, Medanta, The Medicity Hospital, Gurgaon, India
5. Pediatrics Department, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia; kalhasan@ksu.edu.sa
6. Critical Care Department, King Saud University Medical City, King Saud University, Riyadh

* Correspondance: jkari@kau.edu.sa (JAK) , dr.m.a.shalaby@gmail.com (MAS)
** **The first two authors** have contributed equally to this manuscript.

Abstract:

Background: COVID-19 is a respiratory disease that eventually became pandemic with 300 million people infected around the world. Alongside the improvement in COVID-19 management and vaccine development, identifying biomarkers for COVID-19 has recently reported to help in early prediction and managing severe cases which might improve outcome. The Aim of our study was to find out if there is any correlation between clinical severity and elevated hematological and biochemical markers in Covid-19 patients and its effect on the outcome

Methods: We have collected data retrospectively of socio-demographic, medical history, biomarkers, and diseases outcome from five hospitals and health institutions in the Kingdom of Saudi Arabia.

Results: Pneumonia was the most common presentation of COVID 19 in our cohort. All biomarkers (D-Dimer, CRP, troponin, LDH and ferritin) except for the mean lowest white blood cells were found to have significant correlation ($p<0.05$) with worse COVID-19 disease outcomes. There was a sig-nificant association between the inflammatory biomarkers and the disease severity of COVID 19 patients ($p<0.001$). Patients with evidence of severe respiratory disease particularly who required mechanical ventilation (MV) had higher biomarkers, when compared to those with stable respiratory condition ($p<0.001$).

 doi:10.20944/preprints202211.0079.v1

Conclusion: Identifying biomarkers predicts outcome for COVID-19 patients and may significantly help in the management.

1. Introduction

COVID-19 is a type of respiratory disease that rapidly became pandemic around the world [1]. It triggered a great effect across the world in several aspects such as implementation of lockdowns, social distancing, and travel restrictions . While the majority of infected people have mild symptoms , around 20% of all COVID-19 patients experience severe symptoms that include hemodynamic instability, respiratory failure, hypoxia, and failure of multiple organs [2]. Ventilation equipment and oxygenation supports are often required for severe cases [3].

It is reported that around 30% of the total severe cases eventually lead to death, as compared to low mortality in those presented with mild symptoms [1]. It was also noted that genetic diversity and extreme recombination rates of different coronaviruses known (SCoV, MERS_CoV, and SCoV2) implies that more outbreaks will possibly occur, leading to diverse outcomes in patients [4]. Patients that had serious COVID 19 experienced pneumonia showing CT scan-ground glass opacity, pneumonitis, and lung damages [5-7]. Multisystem inflammatory syndrome (MIS) is a type of extra-pulmonary complication more commonly present in the younger population that acquired COVID-19 [8,9]. Previous reports have described MIS laboratory features in children (MIS-C) that have relationship to the known hyperinflammatory syndrome [10].

Clinical assessments on COVID-19 patients must be done to identify those that are at-risk. Laboratory biomarkers could present information that significantly affects the patient care quality.

Biomarkers are quantifiable biochemical substances utilized for recognizing and indicating the ailment's presence and severity [11,12]. These markers could be used in early recognition of severe cases and\or identification who are at-risk. On the other hand, they can also be sorted into categories such as 1) immunological and inflammatory host immune response markers, 2) hematological abnormality markers, and 3) end-organ injury and systemic response markers [13]. One type of biomarkers is molecular biomarker in the form of genes, proteins, glycans, or metabolites of which are utilized for evaluation of disorder and its treatment, and contribute to expansion of biomedical development [1].

It was reported that there were changes in hematology and biochemical parameters including lymphocyte count, neutrophil count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR). while there were also findings of high Interleukin 6(IL-6), lactate dehydrogenase (LDG), high blood sugar and gamma-glutanyl transferase (GGT), in more severe course of COVID-19 patients [14-18].

The Aim of our study was to investigate the correlation between clinical severity and elevated hematological and biochemical markers in Covid-19 patients and also if these changes can predict the outcome. This might guide clinicians to identify severe cases and provide early and appropriate management.

2. Materials and Methods

Study Design and Setting

The current research was designed to study common inflammatory biomarkers and its relation to outcomes in patients with COVID-19 infection. This retrospective cohort multicenter study was carried out in five hospitals and health institutes in the Kingdom of Saudi Arabia (KSA;King Abdulaziz University Hospital, King Saud University Medical City,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0079.v1

East Jeddah Hospital, King Fahd Medical City, and Prince Mohammed bin Abdulaziz Hospital). All These hospitals and centers are qualified to receive and treat COVID-19 patients.

Subjects and Methods:

We have revised the data of all patients admitted to different units of participating hospitals (emergency room, medical wards(adult and pediatric) and different intensive care units over the period of March 2020 to July 2020.The COVID-19 infection was confirmed using a real-time reverse transcription polymerase chain reaction(rRT-PCR) test for the qualitative detection of nucleic acid from SARS-COV-2 from respiratory tract specimens(Nasopharyngeal swabs or endotracheal aspiration). All positive patients either with initial positive swab or those initially negative but turned positive with subsequent repeated swab were included. Patients with any medical conditions or receiving any medication might affect level of tested markers and those with insufficient data were excluded.

We have collected baseline, demographic and clinical data of all recruited patients (adult and pediatric population): gender, age, body mass index, associated comorbidities(diabetes meliteus, hypertension, renal disease, cardiac disease, respiratory disease, hematology and oncology diseases , post-transplant, central nervous system disorders, and humanin immunedefiancy virus (HIV) infection (table 1). The presenting symptoms and signs are listed in table 2.

Table 1: Baseline Patients' demographic and disease characteristics.

Characteristics	Estimate
Age – yr./mean (SD)	46.2 (19.5)
Age – yr./ median (IQR)	48 (34-60)
Male Sex	680 (64.6)
BMI – mean (SD)	28.1 (11.3)
BMI – median (IQR)	27.0 (23.7-30.9)
Comorbidities – No. (%)	
Diabetes	379 (36.0)
Hypertension	344 (32.7)
Renal disease	92 (8.7)
Cardiac disease	154 (14.6)
Respiratory disease	122 (11.6)
Hematology disorder	31 (3.0)
Oncology disorder	30 (2.9)
Post-transplant	6 (0.6)
CNS disorder	4 (1.8)
HIV infection	2 (0.9)
Any comorbidity	605 (57.5)

 doi:10.20944/preprints202211.0079.v1

Abbreviations: BMI, body mass index; CNS, central nervus system; HIV, human immunodeficiency virus.

Table 2: Presenting signs and symptoms.

Characteristics	% (95% CI)
Symptoms	
Fever	72.4 (69.6 – 75.0)
Cough	66.7 (63.7 – 69.5)
Dyspnea	56.4 (53.4 – 59.4)
Diarrhea	20.1 (17.7 – 22.7)
Headache	6.2 (4.8 – 7.8)
Muscle Pain	5.2 (4.0 – 6.7)
Skin rash	0.9 (0.4 – 1.6)
Flu like symptoms	14.3 (12.3 – 16.6)
Any Symptom	93.3 (91.6 – 94.7)
Signs	
Fever	53.9 (50.9 – 57.0)
Mild respiratory distress	33.9 (31.0 – 36.9)
Severe respiratory distress	19.6 (17.2 – 22.1)
Heart failure	2.6 (1.7 – 3.7)
Hematemesis	0.6 (0.2 – 1.2)
Dehydration	3.5 (2.5 – 4.8)
Tonsilitis	5.9 (4.5 – 7.5)
No clinical signs	14.7 (12.6 – 17.0)

The following laboratory findings of all patients were revised: haemoglobin (HGB), white blood cells (WBCs)counts, Platelets counts, c-reactive protein (CRP),ferritin, fibrinogen, and D.Diamer,.

Definitions:

Hypoxia was defined as state of decreased oxygen delivery in sufficient amounts at tissues level to maintain adequate homeostasis guided with clinical and laboratory parameters such as decrease oxygen saturation, increasing oxygen requirement and evidence of respiratory failure.

 doi:10.20944/preprints202211.0079.v1

Pneumonia defined as clinical signs and or radiological signs of pneumonia.

KDIGO Definition was used to define Acute kiney injury as an increase in serum Creatinine level to more than 0.3 mg\dl(26.5mmol\L) within48 hrs \increase in serum creatine more than 1.5 timesof basaline and\or reduction of urine output to less than 0.5 ml\kg\hr.[19].

Abnormal low level of any laboratory or inflammatory markers referred to lowest blood level measured during admission in comparison with the reference of institutional labs. in same way abnormal high level of any laboratory or inflammatory markers refer to highest blood level measured during admission in comparison with the reference of institutional labs.

According to the principles of Helsinki Declaration and Ethical commite rules ; the protocol was revised and approved by ethical committee at king abdulaziz university hospital (NO.:….) The privacy and confidentiality of the patients were strictly observed. All data collected was kept in a secure place.

Ethical approval was granted by the Research Ethics Committee (CM-REC) at King abdulaziz university Hospital (Ref. no. 20/0337/IRB).

No conflict of interest was associated with this study.

Statistical Analysis

This research was analyzed and visually presented using IBM SPPS ver. 23 (IBM Corp., Armonk, N.Y., USA) and using GraphPad Prism version 8 (GraphPad Software, Inc., San Diego, CA, USA), respectively. The features of the research variable were defined using a simple descriptive statistic (counts, percentages, mean and standard deviations). In addition, reliability analysis was performed showing a favorable Alpha Cronbach value of > 0.7. Independent t-test was utilized for comparison of ≥ two group means, while One-way ANOVA with Least Significant Difference (LSD) was employed as a post hoc test was used. Pearson's correlation coefficient was also utilized for correlation of variables The normal distribution assumption was used in these tests. Receiver Operating Curves(ROC) were used to compare the ability of highly significant biomarkers to diagnose severe unstable COVID-19 patients. Finally, the null hypothesis was discarded with values < 0.05.

3. Results

We reviewed the data of 1232 patients admitted with COVID-19 positive. We have excluded 179 patients due to either insufficient data or because subjects had medical conditions or were receiving medications which might compromise level of biological markers. The study recruited 1053 subjects (64.6% males). Fig(1). Socio-demographic characteristics of the included subjects in the study is listed in table 1 .

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0079.v1

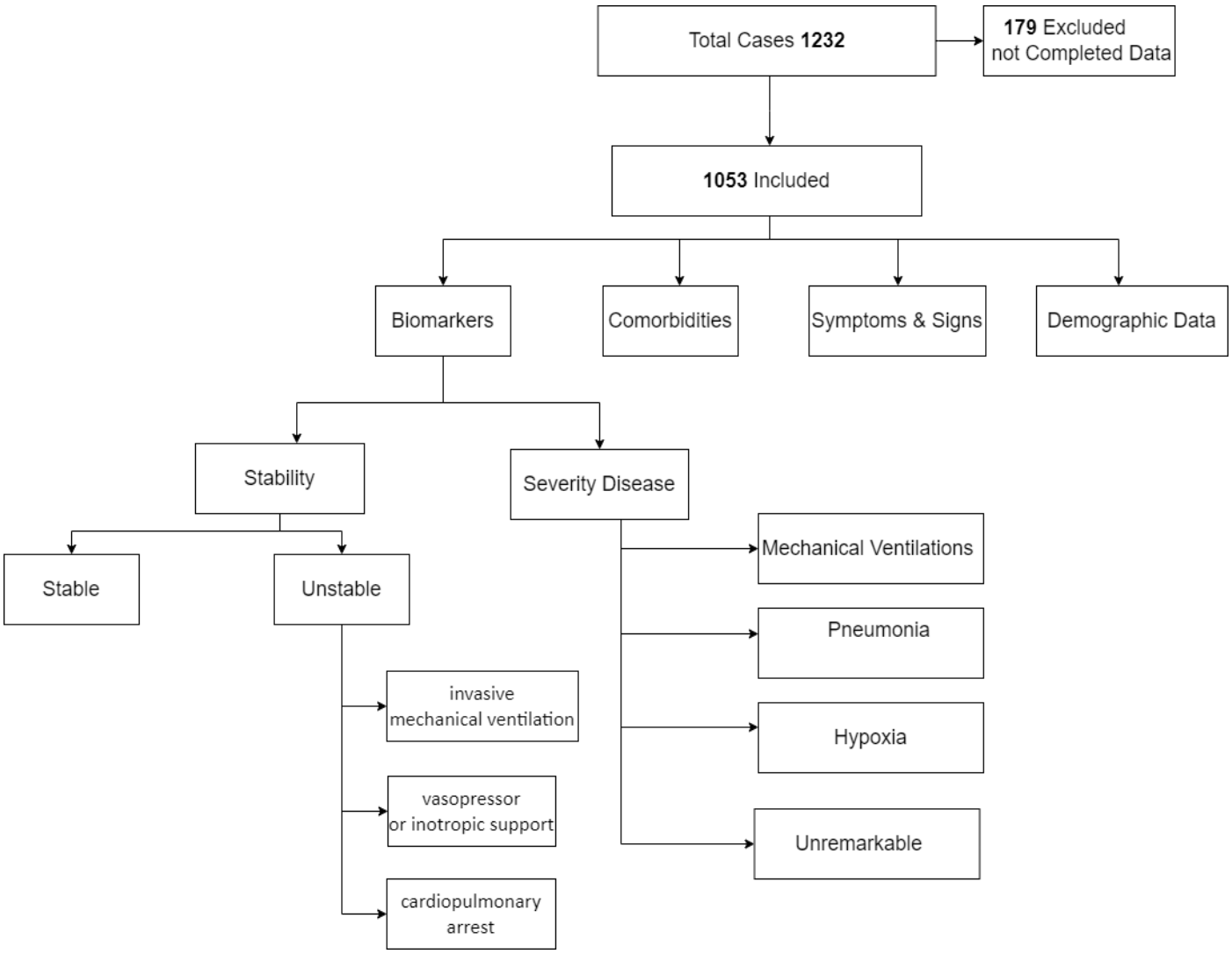
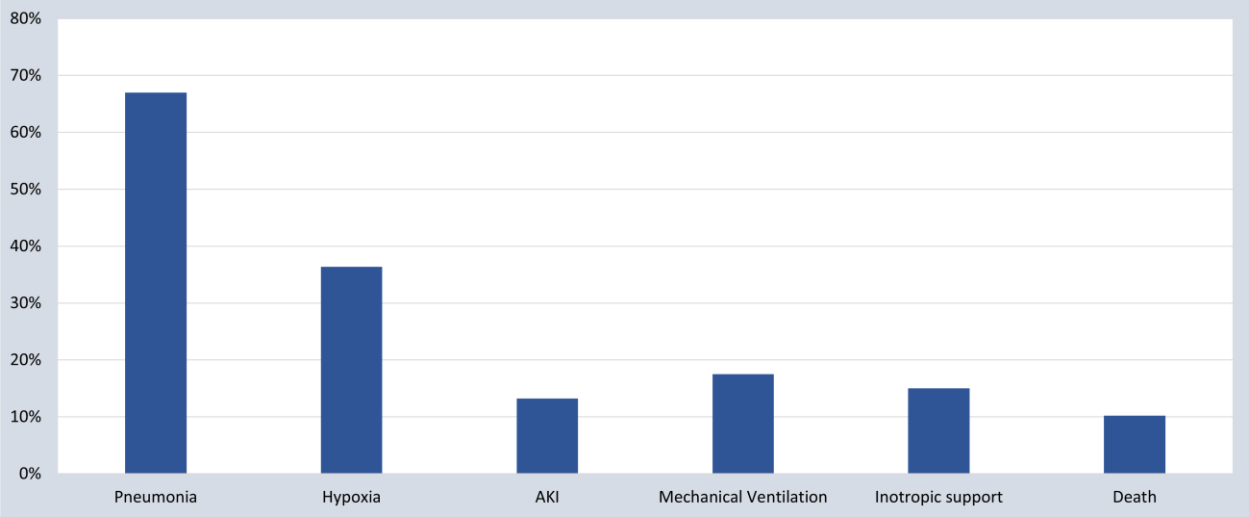


Figure 1: Study Flowchart

More than half of our cohort (57.5%) had at least one of comorbidity. Diabetes mellitus was the most common comorbidity (36%) followed by hypertension(32.7%) ,cardiac disease (14.6%), respiratory disease (11.6%), and renal disease (8.7%).

Presenting signs and symptoms of the studied patients is shown in table 2. The majority (93.3%) of included patients were symptomatic .The most common reported symptom was fever (72.5%, 69.6 – 75.0), followed by respiratory symptoms (cough (66.7%, 63.7 – 69.5) , dyspnea (56.4%, 53.4 – 59.4) and flu like symptoms in almost 14%). Gastrointestinal symptoms were reported in 20.1% mainly in younger age group. Similarly fever was observed as the commonest clinical sign in more than half of studied subjects (53.9%, 50.9 – 57.0), followed by one-third having mild respiratory distress (33.9%, 31.0 – 36.9), and nearly one-fourth with severe respiratory distress (19.6%, 17.2 – 22.1). On the other hand, we looked at severe organs involvement and failure as an indicator of COVID-19 disease severity and outcomes (Figure 2). Results revealed that pneumonia was the most prominent disease manifestation , followed by the hypoxia, mechanical ventilation, inotropic support, AKI and death

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0079.v1

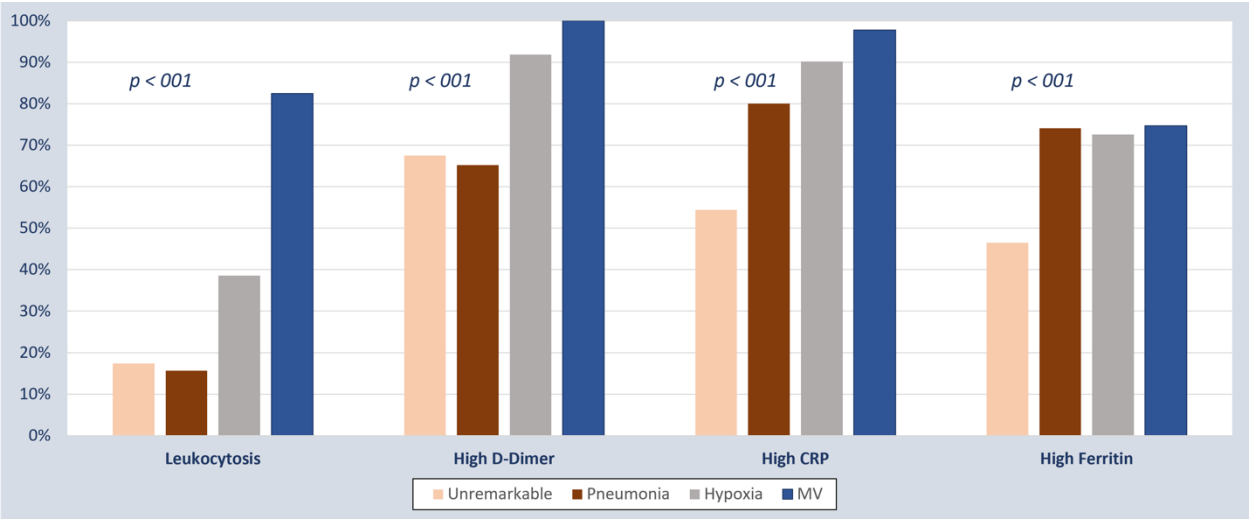


Abbreviations: AKI, acute kidney injury.

Figure 2: COVID-19 Disease Severity and Outcomes.

The Biomarkers associated with worse COVID-19 disease outcomes is shown in table 3. All biomarkers except for the mean lowest WBC were found to be significantly associated with worse COVID-19 disease outcomes ($p < 0.05$). More specifically, significantly lower estimates of mean hemoglobin, and mean platelet count were reported for patients with unstable outcome in comparison with those having stable outcome. Also, significantly higher estimates of, highest mean value of the following markers during admission: WBC, PT, APTT, INR, , fibrinogen, , D-Dimer, , CRP, , and ferritin, were more commonly observed in patients with unstable outcome in comparison to patients who had stable outcome. Also, results revealed significant association between the inflammatory biomarkers and the disease severity of the patients ($p<0.001$). Significantly higher number of patients who need mechanical ventilation (MV) and have worse disease severity and outcome had abnormal biomarkers when compared to patients experiencing pneumonia and hypoxia (figure 3).

The ROC curve (figure 4) showed that that high WBC counts, high D.Dimer and high ferritin is more sensitive predictive markers than CRP in diagnosis of unstable severe COVID-19 .(AUC is 0.85, 0.87, 0.62 with p. value less than 0.001 while for CRP. AUC is 0.61 with p value of 0.64).



Abbreviations: CRP, C reactive protein.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0079.v1

Figure 3 : Inflammatory Biomarkers among COVID-19 Patients with Different Disease Severity, Categorized Based on Respiratory Involvement

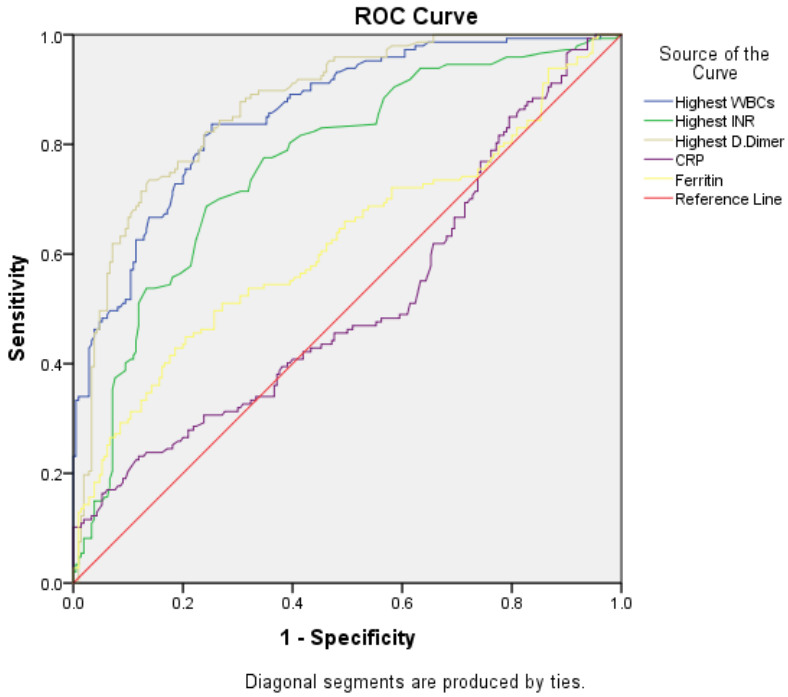


Figure 4.

Table 3: Biomarkers Associated with Worse COVID-19 Disease Outcomes.

Biomarkers	Stable		Unstable*		P Value
	Estimate	95% CI	Estimate	95% CI	
Hemoglobin (mean)$	12.7	12.5 – 12.8	10.9	10.4 – 11.3	<0.001
Highest WBC (mean)@	8.8	8.5 – 9.1	18.0	16.6 – 19.3	<0.001
Lowest WBC (mean) $	6.0	5.8 – 6.2	7.4	6.8 – 7.9	0.241
Platelet (mean) $	261	251 – 270	205	184 - 224	<0.001
PT (mean) @	13.8	13.7 – 14.0	19.4	17.3 – 21.4	<0.001
APTT (mean) @	37.9	36.7 – 39.2	76.9	69.8 – 84.0	<0.001
INR (mean) @	1.11	1.09 – 1.13	1.54	1.39 – 1.69	<0.001
Fibrinogen (mean) @	81	55 – 106	674	569 - 778	<0.001
D-Dimer (mean) @	2.4	1.5 – 3.3	16.3	13.3 – 19.2	<0.001
CRP (mean) @	32.3	28.7 – 35.9	82.1	68.6 – 95.6	<0.001
Troponin I (mean) @	5.3	3.9 – 7.0	3.0	1.7 – 4.4	0.049
Ferritin (mean) @	583	506 – 659	1409	1142 - 1675	<0.001
LDH (mean) @	383	365 – 402	931	804 - 1057	<0.001
ALT (mean) @	55	51 – 59	218	145 - 290	<0.001
AST (mean) @	51	47 - 55	235	153 - 316	<0.001

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0079.v1

Creatinine (mean) [@]	96	86 - 105	348	297 - 399	<0.001
GFR (mean) [$]	84	82 - 87	47	41 - 52	<0.001

Abbreviations: WBC, white blood count; PT, prothrombin time; APTT, partial thromboplastin time; INR, international normalized ratio; CRP, C reactive protein; LDH, lactate dehydrogenase; ALT, alanine transaminase; AST, aspartate transaminase; LFT, liver function test; GFR, glomerular filtration rate.

Notes: *Unstable indicate requirement of invasive mechanical ventilation, vasopressor or inotropic support, and or cardiopulmonary arrest. [$]Lowest blood level measured during admission. [@] Highest blood level measured during admission.

4. Discussion

In this multicentric study with 1053 subjects; we found that most of hospitalized patients due to COVID-19 are male (64.6% of patients).This is similar to previous studies; W.Guan et.al reported that 58.1% of affected patients were male[20]. Risk of death was also reported to be higher in male patients [21] Which might indicate biologic risk determinants as important factor in COVID-19 disease severity.

In our study, we found that 57.5% of all patients had at least one of comorbidity, with diabetes being the commonest,. This is similar to several previous studies ; metanalysis of 48 studies revealed that diabetes, hypertension , cardiovascular disease, renal disease and malignancies are associated with high incidence of death in COVID-19 patients[22].

Fever and respiratory symptoms were very common in our cohort. In a previous retrospective study, we looked at risk factors related to COVID-19 death among 229 critically-ill patients in five hospitals in KSA. We have found that signs and symptoms presented by hospitalized patients -who had died- did not substantially differ when compared to those who survived. Kidney disease, cardiac disease, and diabetes were substantially correlated with in-hospital mortality. [23]. Another retrospective study of 439 COVID-infected subjects from a single center in Riyadh had observed associated comorbidities such as diabetes, vitamin D deficiency, hypertension, and obesity. While higher death rate was observed among diabetic patients as compared to non-diabetic patients, smoking, old age, β-blocker use, congestive heart failure, higher creatinine, occurrence of bilateral lung infiltrates, and severe vitamin D deficiency, were deemed as more substantial predictors of worse outcomes. [24]

Biomarkers were correlated with worse COVID-19 disease outcomes. This is online with previous reports. A systematic review of 52 articles involving 6,320 COVID 19-positive patients revealed that elevated levels of neutrophil count, WBC, prolonged PT, ESR, D-dimer, fibrinogen, procalcitonin, IL-6, and IL-10 can more significantly progress to a more serious form of COVID-19 infection. Similarly, elevated D-dimer, neutrophils, WBCs, and prolonged PT are substantially associated with intensive care admission. On the other hand, mortality was linked with high CRP, IL-6, neutrophil, D-dimer level [24]. Another systematic review involving 4848 COVID-positive patients from 23 studies suggested that severe COVID-infected patients have elevated CRP, procalcitonin, LDH and D-dimer, but lower levels of albumin than those with non-severe COVID-19 infections [25]. Additionally, We have reported previusly that elevated APTT, INR, ferritin, and acidosis were the independent factors that influence mortality among critically-ill COVID-infected participants.[23]. In addition, cardiac biomarkers such as N-terminal pro-B-type

 doi:10.20944/preprints202211.0079.v1

natriuretic peptide (NT-proBNP) and notably high-sensitive cardiac troponin (hs-cTn) can also be considered as key prognostic predictors among COVID 19-infected patients [26]. A meta-analysis research involving 17,794 COVID19-infected subjects had revealed that adverse outcomes were developed by patients with elevated AST and cardiac troponin I levels [29],this is might be consistent to some extent with our study where we found that high level of troponin I is significantly correlated with hemodynamically instability in COVID-19 patients.

Furthermore, a systematic review involving 1735 patients from 21 studies characterized inflammatory markers to compare non-severe/severe COVID-19 against MIS-C, non-severe against severe MIS-C, and MIS-C across different age ranges. Patients with MIS-C had reduced absolute lymphocyte count (ALC) and elevated absolute neutrophil count (ANC), CRP, and D-dimer levels when compared with non-severe COVID19-infected patients. On the other hand, patients with MIS-C had elevated ESR as well as reduced platelet count (PLT) and LDH when compared with severe COVID19-infected patients. Patients with non-severe MIS-C had substantially reduced levels of CRP, ANC, WBC, ferritin, and D-dimer than patients with severe form of MIS-C. Adolescents and older children with MIS-C were found to have elevated ferritin and CRP as compared to children aged between 0 to 5 years old with MIS-C [10]. A study involving 6026 COVID-19infected patients from Hafar Al-Batin and Riyadh cities, with mortality of 23% , revealed that mortality is significantly influenced by older age as well as increased neutrophil and WBC count, and D-dimer level [27]. Another single-center study of 249 COVID-19 patients observed that mortality was substantially linked with augmented procalcitonin, CRP, AST, serum potassium, neutrophil and WBC count, PT, and activated PT in participants with abnormal X-ray results.

We have observed that high LDH, alanine aminotransferase and aspartate aminotransferase are associated with severe and unstable COVID-19 patients. Alguwaihes et al. reported that elevated blood glucose and creatinine level, increased alanine aminotransferase and neutrophil count, was significantly associated with ICU admission[24]. Similarly, Beairwa et.al. stated that lowered LDH, alanine aminotransferase, and aspartate aminotransferase levels has been observed to have substantial correlation with COVID19-infected patient mortality [14] and this could be explained by that liver affection which might happen as part of multiorgan system failure in severe cases .

Our study showed the distribution of inflammatory biomarkers among COVID-19 patients with various severity with significant correlation between the inflammatory biomarkers and the patients disease severity. A higher number of patients who required mechanical ventilation (MV) because of disease severity had abnormal biomarkers such as leukocytes, high D-Dimer, high CRP, and high ferritin. Previous study of 352 critically ill COVID 19 -infected patients in Riyadh revealed that about 56.8% were mechanically-ventilated patients upon ICU admission having peripheral oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio of 158 ± 32. Decreased SpO2/FiO2 ratio, active smoking, old age, pulmonary embolism, as well as heightened D-dimers and lactate were deemed as significant predictors of mortality [28].

ROC curve showed that highest WBCS, high D.Diamer and high ferritin is more sensitive to diagnose severe unstable COVID19 cases than CRP . Elkhalalifa et.al .published data using ROC curve which showed that D.Diamer is important marker for patients hospitalized with severe and unstable COVID-19 patients(29). While Manuela et al who also used ROC curve reported that high CRP can predict worsening of clinical condition.(30).

5. Conclusions

Identifying biomarkers for COVID-19 patients may significantly help in managing the affected patients especially the immune-compromised population. In addition, these biomarkers could be of valuable help in screening patients with varying severity of COVID-19 infection. However, more quantitative studies on the threshold levels of these biomarkers are required to continuously monitor disease progression. As such, dynamic monitoring of these biomarkers as well as longer follow-up duration are recommended for further understanding of COVID-19 prognosis.

Funding: None

Data Availability Statement: Data are available on request

Acknowledgments.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chen, C.H.; Lin, S.W.; Shen, C.F.; Hsieh, K.S.; Cheng, C.M. Biomarkers during covid-19: Mechanisms of change and implications for patient outcomes. *Diagnostics (Basel)* **2022**, *12*, doi:10.3390/diagnostics12020509.
2. Wu, Z.; McGoogan, J.M. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in china: Summary of a report of 72 314 cases from the chinese center for disease control and prevention. *Jama* **2020**, *323*, 1239-1242, doi:10.1001/jama.2020.2648.
3. Badulak, J.; Antonini, M.V.; Stead, C.M.; Shekerdemian, L.; Raman, L.; Paden, M.L.; Agerstrand, C.; Bartlett, R.H.; Barrett, N.; Combes, A.; et al. Extracorporeal membrane oxygenation for covid-19: Updated 2021 guidelines from the extracorporeal life support organization. *Asaio j* **2021**, *67*, 485-495, doi:10.1097/mat.0000000000001422.
4. Su, S.; Wong, G.; Shi, W.; Liu, J.; Lai, A.C.K.; Zhou, J.; Liu, W.; Bi, Y.; Gao, G.F. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol* **2016**, *24*, 490-502, doi:10.1016/j.tim.2016.03.003.
5. Gogate, N.; Lyman, D.; Bell, A.; Cauley, E.; Crandall, K.A.; Joseph, A.; Kahsay, R.; Natale, D.A.; Schriml, L.M.; Sen, S.; et al. Covid-19 biomarkers and their overlap with comorbidities in a disease biomarker data model. *Brief Bioinform* **2021**, *22*, doi:10.1093/bib/bbab191.
6. Nicholls, J.M.; Poon, L.L.; Lee, K.C.; Ng, W.F.; Lai, S.T.; Leung, C.Y.; Chu, C.M.; Hui, P.K.; Mak, K.L.; Lim, W.; et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* **2003**, *361*, 1773-1778, doi:10.1016/s0140-6736(03)13413-7.
7. Zhou, P.; Yang, X.L.; Wang, X.G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.R.; Zhu, Y.; Li, B.; Huang, C.L.; et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, *579*, 270-273, doi:10.1038/s41586-020-2012-7.
8. Noval Rivas, M.; Porritt, R.A.; Cheng, M.H.; Bahar, I.; Arditi, M. Covid-19-associated multisystem inflammatory syndrome in children (mis-c): A novel disease that mimics toxic shock syndrome-the superantigen hypothesis. *J Allergy Clin Immunol* **2021**, *147*, 57-59, doi:10.1016/j.jaci.2020.10.008.
9. Samprathi, M.; Jayashree, M. Biomarkers in covid-19: An up-to-date review. *Front Pediatr* **2020**, *8*, 607647, doi:10.3389/fped.2020.607647.
10. Zhao, Y.; Yin, L.; Patel, J.; Tang, L.; Huang, Y. The inflammatory markers of multisystem inflammatory syndrome in children (mis-c) and adolescents associated with covid-19: A meta-analysis. *J Med Virol* **2021**, *93*, 4358-4369, doi:10.1002/jmv.26951.

11. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther* **2001**, *69*, 89-95, doi:10.1067/mcp.2001.113989.
12. Robb, M.A.; McInnes, P.M.; Califf, R.M. Biomarkers and surrogate endpoints: Developing common terminology and definitions. *Jama* **2016**, *315*, 1107-1108, doi:10.1001/jama.2016.2240.
13. Yang, L.; Xie, X.; Tu, Z.; Fu, J.; Xu, D.; Zhou, Y. The signal pathways and treatment of cytokine storm in covid-19. *Signal Transduct Target Ther* **2021**, *6*, 255, doi:10.1038/s41392-021-00679-0.
14. Bairwa, M.; Kumar, R.; Beniwal, K.; Kalita, D.; Bahurupi, Y. Hematological profile and biochemical markers of covid-19 non-survivors: A retrospective analysis. *Clin Epidemiol Glob Health* **2021**, *11*, 100770, doi:10.1016/j.cegh.2021.100770.
15. Kumar, R.; Singh, V.; Mohanty, A.; Bahurupi, Y.; Gupta, P.K. Corona health-care warriors in india: Knowledge, attitude, and practices during covid-19 outbreak. *J Educ Health Promot* **2021**, *10*, 44, doi:10.4103/jehp.jehp_524_20.
16. Martins-Filho, P.R.; Tavares, C.S.S.; Santos, V.S. Factors associated with mortality in patients with covid-19. A quantitative evidence synthesis of clinical and laboratory data. *Eur J Intern Med* **2020**, *76*, 97-99, doi:10.1016/j.ejim.2020.04.043.
17. Tian, S.; Liu, H.; Liao, M.; Wu, Y.; Yang, C.; Cai, Y.; Peng, Z.; Xiao, S.Y. Analysis of mortality in patients with covid-19: Clinical and laboratory parameters. *Open Forum Infect Dis* **2020**, *7*, ofaa152, doi:10.1093/ofid/ofaa152.
18. Wang, K.; Qiu, Z.; Liu, J.; Fan, T.; Liu, C.; Tian, P.; Wang, Y.; Ni, Z.; Zhang, S.; Luo, J.; et al. Analysis of the clinical characteristics of 77 covid-19 deaths. *Sci Rep* **2020**, *10*, 16384, doi:10.1038/s41598-020-73136-7.
19. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury . Nephron Clin Pract 120:c179–c184
29. Toraih, E.A.; Elshazli, R.M.; Hussein, M.H.; Elgaml, A.; Amin, M.; El-Mowafy, M.; El-Mesery, M.; Ellythy, A.; Duchesne, J.; Killackey, M.T.; et al. Association of cardiac biomarkers and comorbidities with increased mortality, severity, and cardiac injury in covid-19 patients: A meta-regression and decision tree analysis. *J Med Virol* **2020**, *92*, 2473-2488, doi:10.1002/jmv.26166.
20. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032 PMID: 32109013
21. Takahashi T, Iwasaki A. Sex differences in immune responses. Science. 2021; 371(6527):347–8. https://doi.org/10.1126/science.abe7199 PMID: 33479140 .
22. Taylor, E.H.; Marson, E.J.; Elhadi, M.; Macleod, K.D.M.; Yu, J.C.; Davids, R.; Boden, R.; Overmeyer, R.C.; Ramakrishnan, R.; Thomson, D.A.; et al. Factors associated with mortality in patients with COVID-19 admitted to intensive care: A systematic review and meta-analysis. Anaesthesia 2021, 76, 1224–1232.
23. Khalid A Alhasan,Mohamed A Shalaby, Mohamad Hani Temsah,Amr S Albanna and Jameela A Kari:Factors That Influence Mortality in Critically Ill Patients with SARS-CoV-2 Infection: A Multicenter Study in the Kingdom of Saudi Arabia.Healthcare 2021,9,1608.
24. Alguwaihes, A.M.; Al-Sofiani, M.E.; Megdad, M.; Albader, S.S.; Alsari, M.H.; Alelayan, A.; Alzahrani, S.H.; Sabico, S.; Al-Daghri, N.M.; Jammah, A.A. Diabetes and covid-19 among hospitalized patients in saudi arabia: A single-centre retrospective study. *Cardiovasc Diabetol* **2020**, *19*, 205, doi:10.1186/s12933-020-01184-4.
25. Hariyanto, T.I.; Japar, K.V.; Kwenandar, F.; Damay, V.; Siregar, J.I.; Lugito, N.P.H.; Tjiang, M.M.; Kurniawan, A. Inflammatory and hematologic markers as predictors of severe outcomes in covid-19 infection: A systematic review and meta-analysis. *Am J Emerg Med* **2021**, *41*, 110-119, doi:10.1016/j.ajem.2020.12.076.

 doi:10.20944/preprints202211.0079.v1

26. Kaufmann, C.C.; Ahmed, A.; Burger, A.L.; Muthspiel, M.; Jäger, B.; Wojta, J.; Huber, K. Biomarkers associated with cardiovascular disease in covid-19. *Cells* **2022**, *11*, doi:10.3390/cells11060922.
27. Alsagaby, S.A.; Aljouie, A.; Alshammari, T.H.; Mir, S.A.; Alhumaydhi, F.A.; Al Abdulmonem, W.; Alshaalan, H.; Alomaish, H.; Daghistani, R.; Alsehawi, A.; et al. Haematological and radiological-based prognostic markers of covid-19. *J Infect Public Health* **2021**, *14*, 1650-1657, doi:10.1016/j.jiph.2021.09.021.
28. Alharthy, A.; Aletreby, W.; Faqihi, F.; Balhamar, A.; Alaklobi, F.; Alanezi, K.; Jaganathan, P.; Tamim, H.; Alqahtani, S.A.; Karakitsos, D.; et al. Clinical characteristics and predictors of 28-day mortality in 352 critically ill patients with covid-19: A retrospective study. *J Epidemiol Glob Health* **2021**, *11*, 98-104, doi:10.2991/jegh.k.200928.001.
29 Ahmed M. Elkhalifa : D.diamer as a predective and prognestic markers among COVID-19 patients.Saudi Med J2022; Vol43(7).
30. Manuela Rizzi, Martina Costanzo,Stelvio Tonello: Prognostic Markers in Hospitalized COVID-19 patients: The role of IP-10 and C-Reactive Protein;Hindawi Disease markers, Volume 2022, article ID3528312.