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Research Article

Immunological and Clinical Implications of Diabetes and/ or Hypertension as Pre-existing Comorbidities in Iraqi Patients with COVID-19

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Abstract:

COVID-19 patients with comorbidities are associated with increased severity of lung injury, intensive care unit and mortality. These comorbidities are commonly hypertension and diabetes. This study investigated the immunological implications of COVID-19 in patients with hypertension and diabetes with the aim of detecting significant implications with the disease severity.Patients between 30 and 65 years, diagnosed as SARS-COV-2 infection admitted to Al-Hussein Teaching Hospital Kerbala, Iraq were recruited. Clinical symptoms were evaluated and laboratory measurement oftotal and differential leukocyte counts, serum levels of D-dimer, interleukin 6 and C-reactive proteinwere conducted.

A total of 150 admitted COVID-19 patients met criteria and were recruited. Evidence of neutrophilia with lymphopenia was observed in patients with comorbidity. Differential neutrophil percentage highest among those with both diabetes and hypertension i.e. 89.58±9.17 %followed by 78.81±9.93 % for diabetic group, then 62.24±14.42 % for hypertensive, and54.25±11.84 % for patients with no comorbidity. Differential lymphocyte percentagewas lowest among those with both diabetes and hypertension i.e. 2.47±1.24 % followed by 14.29±5.29 % for diabetic group, then 26.73±6.53 for hypertensive, and 33.14±9.35 % for patients with no comorbidity, with significant difference with the groups was observed ($p < 0.05$).Levels of D-dimer, IL-6 and C-reactive protein were significantly higher in patients with comorbidities compared to those without ($p < 0.01$). D-dimer and C-reactive protein levels were higher in diabetics, IL-6 inclined towards hypertensive.

The findings indicate significant immunological implications of the pre-existence of diabetes and hypertension among COVID-19 patients which include aggravation of COVID-19 associated immunopathies.

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Introduction

Over two years after the outbreak of a pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the burden of coronavirus infectious disease 2019 (COVID-19) has continuously increased, with about 500 million people infected and over 6 million deaths recorded globally[1]. Interestingly, although the rate of new infections or re-infections of COVID-19 has tremendously reduced in some countries [2] –partly due to widespread vaccinations and strict adherenceCOVID-19 prevention guidelines, the pandemic is far from over and it still pose a considerable threat to global health security and economic stability.

Studies have revealed that COVID-19 patients with "pre-existing condition(s)" are associated with increased severity of lung injury, hospitalization, intensive care unit admission and mortality [3]. The most prevalent comorbidities of COVID-19 are hypertension, diabetes, coronary heart disease, and chronic obstructive pulmonary disease(COPD) [4]. The most prevalent comorbidities among COVID-19 patients, according to various studies, were hypertension and diabetes, with prevalence rates ranging from 12.8% hypertension and 5.3% diabetes[5] to 32.6% hypertension [6] and 35.5% diabetes [7] to as high as 73.8% hypertension [8] and 58% diabetes [9].

The observed high frequency of hypertension among COVID-19 patients is not surprising since majority of hypertensive are the elderly and aged individuals have higher susceptibility of SARS-CoV-2 infection relative to younger ones [10]. However, while the possibility of a causal relationship between COVID-19 infection and hypertension has not been confirmed by researchers, it has been established that the pre-existence of hypertension predisposes COVID-19 patients to severe forms of the disease as well as its associated complications [11]. Their relationship is explained by how the aetiology of COVID-19 and the pathophysiology of hypertension are related. South et al elaborately reviewed this interrelationship where they highlighted SARS-COV-2 - mediated offset of the renin-angiotensin-aldosterone system (RAAS) as the virus binds to and subsequently internalises the angiotensin converting enzyme 2 (ACE2) during viral entry. This shifts the system to a higher angiotensin (Ang) II/ Ang 1-7 ratio which promotes inflammation, sodium retention, oxidative stress, vasoconstriction and hence hypertension[12, 13]. Moreover, the loss of ACE2 in already hypertensive COVID-19 patients may exacerbate the SARS-COV-2 provoked loss of pulmonary function and tissue fibrosis [14, 15].

Also, reduced expression of ACE2 in vascular tissues could promote inflammation and endothelial dysfunction thus exacerbating an existing atherosclerosis and/ or diabetes[16].With a high global prevalence of diabetes, it is important to understand the effects of COVID-19 infection in diabetics. Since ACE2 receptors have also been shown to be expressed in pancreatic islets, and hyperglycaemia has been reported in COVID-19 patients who were not diabetic at time of admission [17, 18], SARS-COV-2 infection may be associated with transient damage to beta cells.

While most studies focus on the RAAS in the context of hypertension and diabetes comorbidity with COVID-19, immunological factors may play significant roles in the widely reported poor COVID-19 outcomes in both diabetic and hypertensive patients. The SARS-COV-2 viral entry triggers inflammatory response through recruitment of T helper cells which produces interferon – gamma that initiates "cytokine storm" and hence acute respiratory distress syndrome (ARDS) [19]. Also, conditions such as hypertension associated lymphopenia[20] as well as IL-6 elevation [21] in diabetes could be more deleterious in COVID-19.

Therefore, the aim of this study was to investigate the immunological implications of hypertension and diabetes in patients suffering from COVID-19 by identifying COVID-19 patients who have diabetes or hypertension or both and evaluating their baseline clinical/ immunological characteristics aimed at identifying potential

management challenges for diabetic or hypertensive individuals who contract COVID-19 infection. The findings of this study would provide useful information that would aid the ease of timely identification of patients who would require prompt special treatment and personalised care in COVID-19 isolation centres.

Methods

This was study a retrospective cross-sectional study conducted on 150 male and female patients aged between 30 and 65 years, who were diagnosed as having SARS-COV-2 infection after positive result from RT-PCR test for SARS-CoV-2 RNA and were admitted to Al-Hussein Teaching Hospital Kerbala, Iraq from 2nd December, 2021 to 30th February, 2022. Ethical approval was obtained from the Hospital Research and Ethics Committee of Al-Hussein Teaching Hospital, Kerbala, Iraq and informed consent was obtained from all the participants as the aim of the study was clearly stated. The inclusion criteria included patients with positive RT-PCR test for SARS-CoV-2 as well as patients aged above 29 years but not more that 65 years of age, while the exclusion criteria included presence of other comorbidities, pregnancy, autoimmune disorders, evidence of COPD, and other immune related diseases.

Information on demography, medical history, chest CT scan, and symptoms were extracted from the recruited patients' medical records.

The presence of clinical symptoms such as fever, fatigue, cough, shortness of breath (SOB) and diarrhoea were evaluated by a physician who was unaware of the patients' comorbidity.

Venous blood samples were collected for whole blood analysis and serum was prepared for serological analysis. Laboratory investigations measuring total leukocyte count (TLC) and differential leukocyte counts of neutrophils, lymphocytes, monocytes, eosinophils and basophils using an automated haematology analyzer (Swelab Alfa Plus haematology analyzer, (Boule Medical AB, Sweden. Levels of D-dimer, interleukin (IL)-6 and C-reactive protein (CRP) were also measured using (Hotgen POCT UPT 3A UP Converting Phospher Immunoassay Analyzer).

Measurements of random blood sugar (RBS) as well as systolic and diastolic blood pressure (BP) were made and the patients were categorized as diabetic or hypertensive based on the American Diabetes Association guidelines [22] and the recommendations of the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [23] respectively, after which they were grouped as follows:

Diabetic: Those with RBS $\geq$ 200 mg/dL but with systolic BP < 140 mmHg and diastolic BP < 90 mmHg.

Hypertensive: Those with systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg but with RBS < 200 mg/dL.

Diabetic & Hypertensive: Those with RBS $\geq$ 200 mg/dL and systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg

None: Those with RBS < 200 mg/dL and systolic BP < 140 mmHg with diastolic BP < 90 mmHg (i.e. no comorbidity).

Statistical analysis

Clinical symptoms which are categorical were expressed as percentages (%) of their respective frequencies within each group. Age, RBS, HbA1c and blood pressure were expressed as mean ± standard deviation (SD) with Student's t test performed to determine statistical significant at $p < 0.05$. Differential leukocyte counts were expressed as their percentagesof the TLC and statistical significant difference between the groups was determinedthrough one-way analysis of variance (ANOVA) followed by Tukey's HSD test. Whilelevels of D-dimer, IL-6 and CRP were presented using box plots and statistical significant difference between the groups was determined through Kruskal-Wallis H test followed by Dunn's multiple comparison tests at $p< 0.01$ and $p < 0.05$. Statistical analysis was conducted using the SPSS 23.0 software.

Results

After the first 150 admitted COVID-19 patients who met the study criteria were recruited, the selection process was halted. The patients consisted of 58 females (38.67%) and 92 males (61.33%), with the mean age of 49.45±9.79 years. The exclusively diabetic patients were 52 (34.67%), exclusively hypertensive patients were 31 (20.67%), and those with diabetes and hypertension were 19 (12.67%) while 48 (32.0%) patients were neither diabetic nor hypertensive.

Table 1 shows how the groups differed with respect to demographic and clinical characteristics. The diabetic group had a mean age of 49.38±7.39 years, hypertensive with a mean age of 53.90±8.83 years and those with both comorbidities were slightly older with a mean age of 55.20±9.03 years, all of which were significantly higher than 43.94±10.27 years observed among patients with no comorbidity ($p < 0.05$). The mean RBS was 239.68±37.11 mg/dL, 158.99±22.72 mg/dL, 278.38±34.63 mg/dL and 146.13 ± 28.98 mg/dL while mean HbA1c was 7.75±1.09%, 5.87±0.44%, 8.51±1.12 % and 5.53±0.38 % for diabetic, hypertensive, diabetic & hypertensive, and none respectively. Similarly, the mean systolic BP was 126.21±5.54 mmHg, 156.70±9.84 mmHg, 164.84±10.75 mmHg, and 120.85±5.36 mmHg while mean diastolic BP was 73.52±5.41 mmHg, 81.90±4.13 mmHg, 89.11±4.03 mmHg and 69.10±5.57 mmHg for diabetic, hypertensive, diabetic & hypertensive, and none respectively.

Table 1: Demographic and clinical characteristics of the patients

	Diabetic (n = 52)		Hypertensive (n = 31)		Diabetic & Hypertensive (n = 19)		None (n = 48)	
	(Mean ± SD)	95% C.I. (Lower - Upper)	(Mean ± SD)	95% C.I. (Lower - Upper)	(Mean ± SD)	95% C.I. (Lower - Upper)	(Mean ± SD)	95% C.I. (Lower - Upper)
Gender (n, %)								
Female	17 (11.33%)		12 (8.00%)		8 (5.33%)		21 (14.00%)	
Male	35 (23.33%)		19 (12.66%)		11 (7.33%)		27 (18.00%)	
Age (years)	49.38 ±7.39*	47.38 - 51.39	53.90±8.83*	57.01 - 50.80	55.20±9.03*	51.14 - 59.26	43.94±10.27	41.03 - 46.84
RBS (mg/dL)	239.68±37.11 *	229.59 - 249.76	158.99±22.72*	150.99 - 166.99	278.38±34.63*	262.81 - 293.96	146.13±28.98	137.93 - 154.33
HbA1c (%)	7.75±1.09*	7.46 - 8.05	5.87±0.44*	5.71 - 6.03	8.51±1.12*	8.00 - 9.02	5.53±0.38	5.43 - 5.64
Systolic (mmHg)	126.21±5.54*	124.71 - 127.72	156.70±9.84*	153.25 - 160.17	164.84±10.75*	160.00 - 169.68	120.85±5.36	119.34 - 122.37
Diastolic (mmHg)	73.52±5.41*	72.05 - 74.99	81.90±4.13*	80.45 - 83.36	89.11±4.03*	87.30 - 90.92	69.10±5.57	67.53 - 70.68

C.I. (Confidence interval); SD (Standard deviation); RBS (Random blood sugar); HbA1c (Glycosylated haemoglobin).

***Statistical significant difference compared to mean value of patients with no comorbidity (None) at P < 0.05.**

The TLC measures as well as the leukocyte differential counts of the patients are graphically presented in Figure 1. The mean TLC (in cells/µL) was highest among those with both diabetes and hypertension i.e. 15248.72±1472.31 followed by 12294.25±2821.46 for diabetic group, then 9491.74±2215.38 for hypertensive, and 8025.93±1407.18 for patients with no comorbidity. Similarly, the diabetic & hypertensive group recorded the highest differential percentage of neutrophils i.e.

89.58±9.17 %, followed by the diabetic group with 78.81±9.93 % while 62.24±14.42 % and 54.25±11.84 % were recorded for hypertensive and none group respectively. Conversely, relative percentages of lymphocytes, monocytes and eosinophils werelowest among those with both diabetes and hypertension (i.e. 5.94±2.32 % lymphocytes, 2.47±1.24 % monocytesand 0.43±0.23 % eosinophils), followed by diabetic group (i.e. 14.29±5.29 % lymphocytes, 4.17±0.81 % monocytes and 1.76±0.66 % eosinophils), then hypertensive (with 26.73±6.53 % lymphocytes, 7.23±1.29 % monocytes and 2.55±0.52 % eosinophils) and the highest relative percentage of33.14±9.35 lymphocytes %, 8.95±1.93 %monocytes and 3.24±0.93 % eosinophils was observed in patients with no comorbidity. One-way ANOVA indicated general statistical significant difference while Tukey's HSD test indicated specific pair-wise significant difference between the groups for TLC, neutrophils, lymphocyte, monocytes and eosinophils with p-value set at < 0.05. There was no significant difference in basophil differential count between the groups (p = 0.063005).

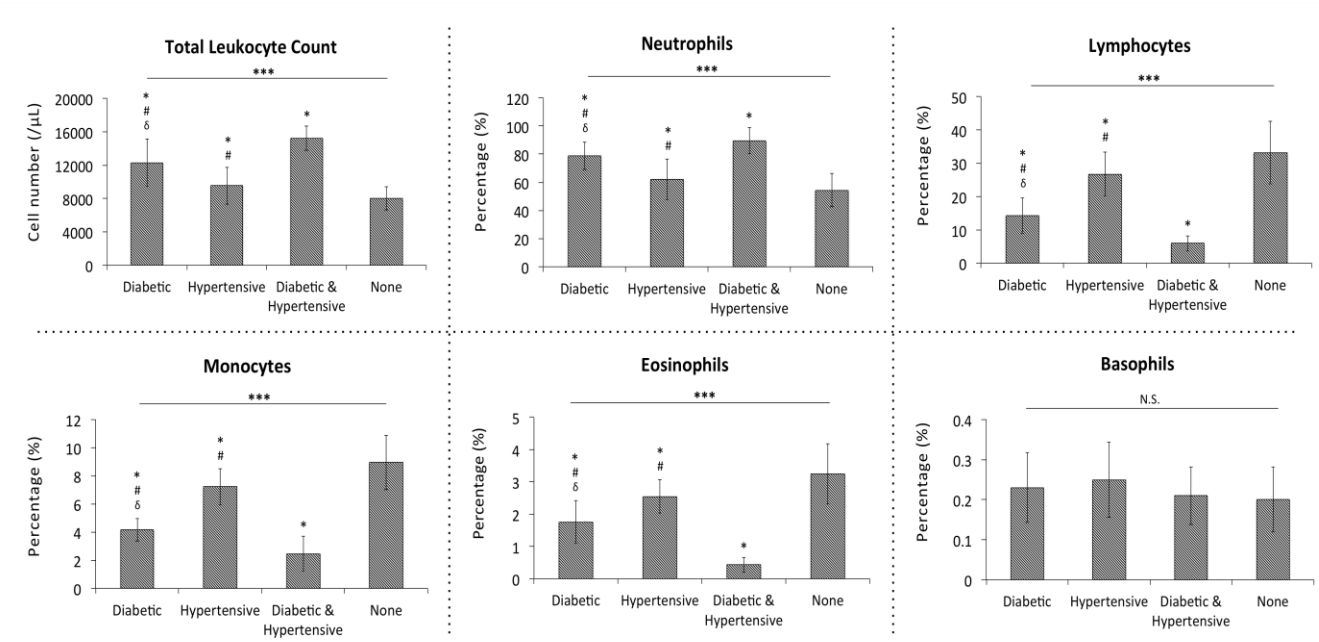

Figure 1: Total leukocyte count and differential leukocyte count of the patients.

The mean TLC and neutrophils were highest among those with both diabetes and hypertension followed by diabetic group, then hypertensive and least in patients with no comorbidity. Conversely, relative percentages of lymphocytes, monocytes and eosinophils were lowest among those with both diabetes and hypertension followed by diabetic group then hypertensive and the highest relative percentage was observed in patients with no comorbidity. One-way ANOVA indicated general statistical significant difference while Tukey's HSD test indicated specific pair-wise significant difference between the groups with p-value set at < 0.05.

***** indicates statistical significance across the groups**
*** indicates statistical significance compared to 'None'**
 # indicates statistical significance compared to 'Diabetics &Hypertensive'
δ indicates statistical significance compared to 'Hypertensive'

Statistical analysis of serum levels of D-dimer, IL-6 and CRP using Kruskal Wallis test followed by Dunn's test for multiple comparisons is graphically presented using box-plots in Figure 2. Levels of D-dimer were significantly higher in patients with diabetes and hypertension as well as those with diabetes only compared to patients with no comorbidity at $p < 0.01$. Significant difference between the hypertensive and none group was only observed at $p < 0.05$. Also D-dimer levels were significantly higher in diabetic & hypertensive group compared to diabetic group and hypertensive group at $p < 0.01$. For IL-6, significantly higher levels were recorded in patients with comorbidities compared to those without ($p < 0.01$). Although IL-16 was not significantly higher in patients with hypertension only, compared to those with diabetes only (at $p < 0.01$ or $p < 0.05$), it was observed to be significantly higher in hypertensive when compare to those with both comorbidities ($p< 0.01$). The highest CRP levels were observed in patients with diabetes and hypertension, with significantly high levels among patients with comorbidities compared to those without ($p < 0.01$) and diabetic patients showing significantly higher CRP levels compared to those with hypertension only ($p < 0.01$).

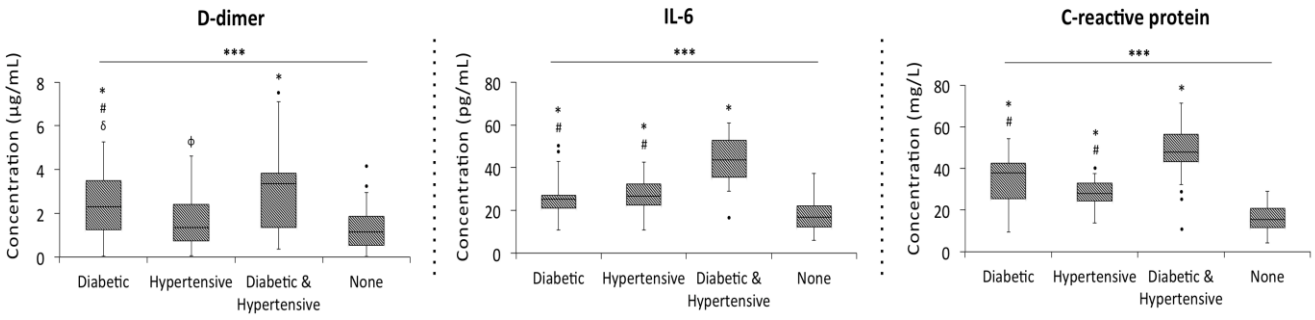

Figure 2: Box plots showing serum levels of D-dimer, IL-6 and CRP in the patients

D-dimer, IL-6 and CRP were higher in patients with comorbidities compared to those without. Levels of D-dimer and CRP were higher in diabetics, while IL-6 inclined towards hypertensive. Kruskal-Wallis H test followed by Dunn's multiple comparison tests was conducted.

***** indicates statistical significance across the groups at $p < 0.01$**
*** indicates statistical significance compared to 'None' at $p < 0.01$**
φ indicates statistical significance compared to 'None' at $p < 0.05$
 # indicates statistical significance compared to 'Diabetics & Hypertensive' at $p < 0.01$
δ indicates statistical significance compared to 'Hypertensive' at $p < 0.01$

Figure 3 shows the frequency distribution of symptoms presented by the patients among the different groups. While most patients presented symptoms of fever, fatigue, cough, SOB and diarrhoea (majority of which were patients with comorbidities), 38 patients were asymptomatic or presented mild symptoms, of which 25 (65.80%) were patients with no comorbidity.

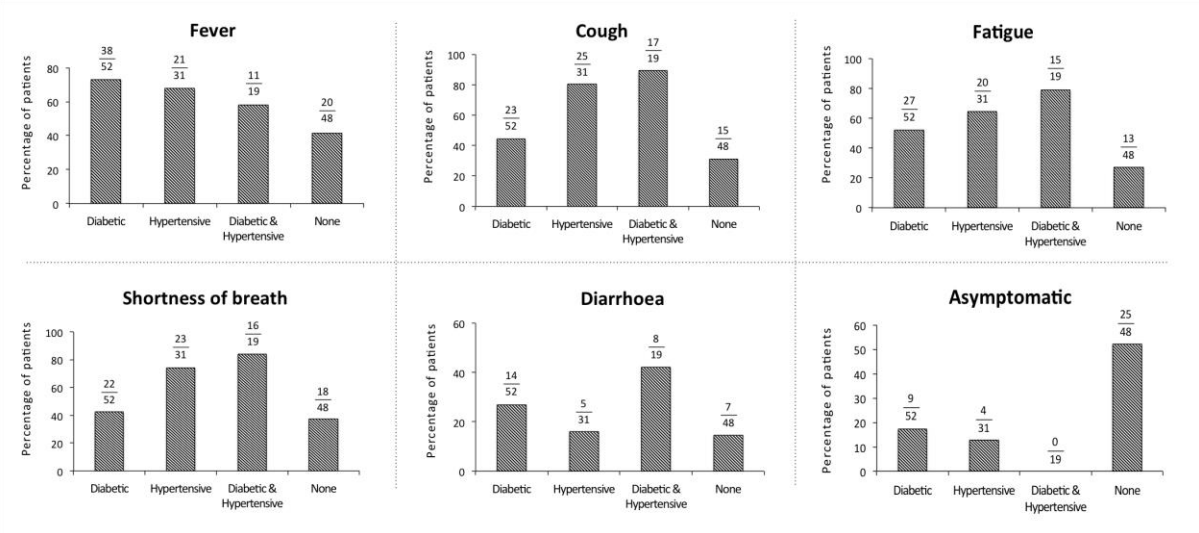

Figure 3: The frequency distribution of symptoms presented by the patients among the different groups

The fraction on each bar chart shows the exact number of patients from each study group who present the particular symptom**.**

Discussion

The growing prevalence rates of diabetes and hypertension in the general population is already alarming. More worrisome however, is their higher prevalence amongCOVID-19 patients, making these two conditions the most important comorbidities of COVID-19. This study sought to investigate the immunological implications associated with these comorbidities among COVID-19 patients in Iraq, aimed towards identifying challenges that may be associated with management of diabetic or hypertensive patients who develop COVID-19 infection. In this study, 68% of the patients were comorbid while those having diabetes exclusively were more than those with hypertension exclusively. Although many studies have reported a higher prevalence of hypertension compared to diabetes among COVID-19 patients [8], Huang et al and Mohamad et al are among few studies that reported higher prevalence diabetes over hypertension among COVID-19 patients [24, 25]. The observed predominance of diabetes in this study could be ascribed to the relatively high prevalence of diabetes in Iraq and the Arab population [26, 27]. Moreover, majority of these patients may be unaware of their diabetic status since this study identified diabetics from elevations in RBS (i.e. ≥ 200 mg/dL) rather than being extracted from medical records.

Despite having an overall mean age of 49.45 years, this study observed age related preponderance in patients with both comorbidities. The non-comorbid patients were the youngest of the study groups with diabetics being relatively younger than hypertensive while the oldest were patients having both diabetes and hypertension with 9 out of the 19 patients aged 60 years and above. Previous studies have reported poorer outcomes in aged COVID-19 patients; with the pre-existence of comorbidities identified as the major culprits [28, 29].

Accumulating body of evidence has established the effect of diabetes as well as hypertension on COVID-19 disease severity with patients having these comorbidities significantly more likely to be critically ill and require admittance into intensive care relative to those without comorbidity [30-32]. The immune system plays a central in the crosslink between diabetes, hypertension and COVID-19. This study observed leukocytosis coupled with neutrophilia, lymphopenia, monocytopenia and eosinopenia in the patients especially amongst those with comorbidity. These outcomes are indicative of an ongoing immune-inflammatory stress [33]. Leucocytosis with neutrophilia has been strongly associated with COVID-19 [34, 35] and with neutrophils accounting for accounting for 50 – 70% of leukocytes, the observed leucocytosis can be ascribed to elevations in neutrophil population after 7 days of COVID-19 symptoms onset[35]. Being the first responders to infection, neutrophils play significant protective roles against fungal and bacterial infections [36]. During viral infection however, it has been suggested that neutrophils interact with other cells to bring about anti-viral protection through activation of cytokine release, degranulation, virus internalization, oxidative burst and establishment of neutrophils extracellular traps [37], thus the recruitment of these polymorph nuclear cells can be triggered in response to SARS-COV-2 infection. However, while neutrophils accumulation may be aimed at ameliorating the viral attack, respiratory burst resulting from excessive activation of these cells induces production of reactive oxygen species like hydrogen peroxide and superoxide radicals that culminate into oxidative stress leading to COVID-19 associated cytokine storm and thrombosis[38, 39]. For these reasons, neutrophilia has associated with ARDS in COVID-19 patients [40]. As observed in this study, lymphopenia has not only been previously reported in COVID-19 patients, it has also been correlated with disease severity and poor prognosis[41, 42]. Tavakolpour et al hypothesized based on literature that inflammatory cytokine storm, exhaustion of T-cells especially, CD4+ and CD8+ cells (which have been shown to exhibit increased expression of pro-apoptotic markers in COVID-19), and SARS-COV-2 interference with T-cell expansion as the underlying causing of observed lymphopenia in COVID-19 [43].

The index that compares neutrophils count with that of lymphocytes is the neutrophil to lymphocyte ratio (NLR), which when high, implies onset of neutrophilia with lymphopenia, and aids better understanding of the implications of diabetes and hypertension on neutrophilia and lymphopenia in COVID-19 patients. High NLR has not only be identified as a biomarker of clinical inflammation in COVID-19 [44], but also as a predictor of incident hypertension [45, 46] and as an indicator of insulin resistance and poor glycaemic control in type 2 diabetes mellitus [47].Moreover, Anurag et al found significantly higher NLR in diabetic as well as in hypertensive COVID-19 patients relative to their non-diabetic or non-hypertensive counterparts [48]. Therefore, the observed high neutrophilia with lymphopenia in patients with comorbidities especially among the diabetic & hypertensive group indicates poor disease outcome relative to those without these comorbidities. Thus supporting the idea that pre-existing diabetes and hypertension contributes to COVID-19 severity.

Serum analysis of D-dimerin this study revealed high values in patients with comorbidities compared to those without. The elevated D-dimer levels inclined more towards diabetic patients than hypertensive; however those having both comorbidities recorded the highest D-dimer levels. Being a by-product of degradation of fibrin and an indicator coagulation and fibrinolysis, D-dimer has been widely recognised as a signal of COVID-19 associated thromboembolism and hence, a biomarker for predicting disease severity and prognosis with elevations in levels of D-dimer in COVID-19 patients with COVID-19 are associated with poor prognosis[49]. Among diabetics, Mishra et al reported significantly higher levels of D-dimer in diabetic COVID-19 patients compared to non-diabetics[50]. Similar to the findings of this study, elevated D-dimer levels

have been reported in hypertensive COVID-19 patients compared to non-hypertensive[51]. However, the present study observed that those with diabetics are more likely to have high D-dimer levels than hypertension. Researches mentioned that persistent hyperglycaemia can result to inflammation and endothelial dysfunction which in turn can lead to thrombus formation [52], could provide an explanation for this observation.

This study also observed high elevations in serum IL-6 levels in patients with comorbidities with the highest recorded values amongst those with both diabetes and hypertension. The importance of IL-6 in the pathophysiology of COVID-19 cannot be overemphasized. This cytokine pleiotropic in nature and has the ability of executing both proinflammatory and anti-inflammatory functions and modulates homeostasis between immunoprotection and immunopathology of viral infections[53]. IL-6 acts as inducer of granzyme B and perforin expression in CD8+ T cells which aids the elimination of viral pathogens and as a thermo-regulator that amplifies anti-viral immunosurveillance through promotion of IL-27 dependent maturation of regulatory T-cells [54-56]. Elevated levels of this cytokine can also promote the differentiation of Th17 cell and resultant production of IL-17 which leads to expression of anti-apoptotic molecules that enhance virus survival in infected cells [57, 58]. Moreover, production of IL-6 by inflammatory monocytes in severe COVID-19 contributes to the formation of cytokine storm[53]. This study also observed those hypertensives are more likely to have high IL-6 relative to diabetics. The presence of evidence suggesting a strong relationship between circulating IL-6 levels and blood pressure directly correlates hypertension with elevated IL-6[59], making hypertensive COVD-19 patients more susceptible to having severe respiratory failure.

The CRP, an acute phase protein secreted in the liver in response to infectious and inflammatory conditions, was observed to be elevated in diabetics, hypertensive as well as those with both comorbidities. While high CRP levels have been reported in COVID-19 patients with diabetes [60] as well as in those with hypertension [61], this study observed that diabetic patients were more likely to have higher CRP levels compared to the hypertensive. It is widely known that chronic hyperglycaemia induces a pro-oxidative and proinflammatory state which could exacerbate the inflammatory cytokine storm, CRP elevations and bring about adverse outcomes in COVID-19 patients [62]. Also high CRP and IL-6 levels have been linked with elevations in NLR which as discussed earlier is a clinical inflammation biomarker that predicts severe illness even at early stages of SARS-COV-2 infection[63]. Moreover, Koh et al reported CRP as a significant mediator of the association between pre-existing diabetes and severe COVID-19 infection [64].

The presentation of major clinical symptoms varied markedly between patients with comorbidity and those without. The major symptoms recorded in this study in order of their predominance were fever, cough, fatigue, shortness of breath and diarrhoea. Interestingly, these are the major sets of symptoms presented by COVID-19 patients during early disease onset as reported by previous studies and are consistent with symptoms of viral infections and pneumonia[65]. Since the presentation of these symptoms were non-mutually exclusive in nature, as a patient could present between one to all major symptoms, it is challenging to ascribe a comorbidity to a particular symptom and hence to disease severity. However, while fever was the most predominant symptom among the diabetic group and non-comorbid patients, cough was dominant in hypertensive and those with diabetes and hypertension. Studies have shown that not all COVID-19 patients show symptoms as some could be asymptomatic or may have mild symptoms [66, 67]. Asymptomatic patients were observed in this study, majority of which were found among patients with no comorbidity, as group-wise distribution of asymptomatic patients were 52% (non-comorbid patients), 17.3% (diabetics), 12.9% (hypertensive) and 0% (diabetics &hypertensive). Therefore, COVID-19 patients with comorbidity of diabetes and/ or

hypertension are more likely to present major symptoms than those without.

Conclusion

In conclusion, the findings of this study indicate that there are significant immunological implications of the pre-existence of diabetes and hypertension among COVID-19 patients which include aggravation of COVID-19 associated immunopathies such as neutrophilia with lymphopenia, elevations in serum D-dimer, IL-6 and CRP levels as well as presentation of major symptoms even during early disease onset. Therefore, COVID-19 patients with diabetes and/ or hypertension are exposed to inflammation and endothelial dysfunction which in turn can lead to thrombus formation, are more susceptible to having severe respiratory failure and present major symptoms than those without; all of which culminates to poor disease outcomes that further worsening of disease severity which are deleterious to prognosis. It is suggested that patients with these comorbidities be given specialised supportive care options with considerations to their pre-existing conditions. Some limitations of this study include, relatively small sample size (n = 150) as the retrospective nature of this study resulted to a smaller population among the respective study groups especially the diabetics &hypertensive group (n = 19). Also type 1 diabetes mellitus were not differentiated from type 2 since both forms of diabetes have been associated with increase in adverse COVID-19 outcomes [68]. It is recommended that future studies can however, put these shortcomings into consideration and carryout follow-up studies to observe the outcomes of the patients with comorbidities.

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