Alterations in several paraclinical indicators among COVID-19 patients in Da Nang city

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ABSTRACT

Background: COVID-19 is associated with diverse clinical and biochemical abnormalities, including renal dysfunction marked by elevated serum urea, a potential prognostic indicator in severe cases. ***Methods:*** A retrospective cross-sectional study analyzed medical records of 284 COVID-19 patients at Da Nang Pulmonary Hospital from September 2021 to April 2022. Serum urea, creatinine, GOT, GPT, and D-dimer levels were assessed. Associations with age, comorbidities, symptoms, and disease severity were evaluated using SPSS 20.0, with $p < 0.05$ considered significant. ***Results:*** Elevated serum urea (>7.5 mmol/L) was observed in 17.6% of patients. Mean urea was 6.39 ± 6.57 mmol/L, creatinine 211.98 ± 287.08 µmol/L, GOT 32.29 ± 18.97 U/L, and GPT 32.82 ± 27.24 U/L. Urea elevation was significantly associated with age >60 years ($p = 0.000$), hypertension ($p = 0.000$), cardiovascular disease ($p = 0.000$), and disease severity ($p = 0.001$), but not diabetes ($p > 0.05$). ***Conclusion:*** Elevated serum urea is prevalent in COVID-19 patients, particularly older individuals with hypertension, cardiovascular disease, or severe disease. Routine urea monitoring may enhance risk stratification and guide management in Vietnam's resource-limited settings.

Keywords: *Serum Urea, D-dimer, COVID-19, Renal Dysfunction, Biochemical Markers*

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has posed unprecedented challenges to global healthcare systems since its emergence in 2019. In Vietnam, Da Nang was an early epicenter, with significant outbreaks in 2020–2021 [1]. COVID-19 presents with a wide clinical spectrum, from asymptomatic infection to critical illness involving acute respiratory distress syndrome (ARDS), coagulopathy, and multi-organ dysfunction [2]. Biochemical abnormalities, including elevated serum urea, creatinine, and liver enzymes, are common in severe cases, reflecting organ damage driven by systemic inflammation, hypoxia, or direct viral effects [3].

Serum urea, a marker of renal function, is frequently elevated in COVID-19, often indicating acute kidney injury (AKI) or prerenal azotemia due to dehydration or hypoperfusion [4]. Cheng et al. (2020) reported that AKI, associated with elevated urea, increased mortality risk by 4.3-fold in COVID-19 patients [5]. Coagulation disturbances, particularly elevated D-dimer,

are also hallmark features, reflecting a hypercoagulable state linked to endothelial dysfunction and microthrombosis [6]. Tang et al. (2020) found elevated D-dimer in 71.4% of non-survivors, underscoring its prognostic value [7]. Other markers, such as GOT and GPT, indicate hepatic involvement, while creatinine elevation signals renal impairment [8].

In Vietnam, data on biochemical changes in COVID-19 patients are scarce, particularly in regional hospitals like Da Nang Pulmonary Hospital, which managed significant caseloads during the pandemic [9]. This study aims to: (1) determine the prevalence of elevated serum urea in COVID-19 patients, and (2) identify associated factors, including age, comorbidities, symptoms, and disease severity, to inform clinical practice in resource-constrained settings.

MATERIALS AND METHODS

Study Design

A retrospective cross-sectional study was conducted, reviewing medical records of COVID-19 patients treated at Da Nang Pulmonary Hospital from September 1, 2021, to April 30, 2022.

Participants

The study included 284 patients with confirmed COVID-19 (via RT-PCR) and complete medical records.

Inclusion criteria: Hospitalized patients with documented serum urea, creatinine, GOT, GPT, and D-dimer levels at admission.

Exclusion criteria: Patients with pre-existing coagulation disorders, pregnancy, or age <18 years.

Records were selected consecutively until the sample size was met.

Sample Size

The sample size was calculated using:

$$n = \frac{z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where: ($Z^2_{(1-\alpha/2)}$ = 1.96) (95% confidence), (p = 0.372) (D-dimer elevation prevalence from He et al., 2021 [10]), (d = 0.07) (margin of error).

The minimum sample size was 184, increased by 10% to 204 for incomplete records.

A total of 284 records were analyzed.

Data Collection

Data included:

Demographics: Age (≤ 60 vs. > 60 years), sex.

Symptoms: Fever, cough, fatigue, dyspnea, etc.

Comorbidities: Hypertension, diabetes, cardiovascular disease, chronic kidney disease, others.

Disease severity: Per Vietnam Ministry of Health guidelines (asymptomatic, mild, moderate, severe) [11].

Biochemical markers: Urea (normal: ≤ 7.5 mmol/L), creatinine (male: 62–120 µmol/L; female: 53 – 106 µmol/L), GOT (≤ 37 U/L), GPT (≤ 40 U/L), D-dimer (≤ 500 µg/L).

Data were collected anonymously using a standardized form.

Statistical Analysis

Data were analyzed using Microsoft Excel and SPSS 20.0. Descriptive statistics included means ± standard deviations (SD), ranges, and frequencies (%). Chi-square tests assessed associations between urea elevation and categorical variables (p-value < 0.05 was considered as significant). ROC analysis evaluated urea's diagnostic performance using Medlab 12.5.

Ethical Issues

The study was approved by the Biomedical

Ethics Committee of Da Nang University of Medical Technology and Pharmacy (No. 2021-09/BB-HĐĐĐ, August 2021) and Da Nang Pulmonary Hospital, adhering to the Declaration of Helsinki. Data were anonymized.

RESULTS

Participant Characteristics

Of 284 patients, 68.7% (195) were female, and 87.3% (248) were ≤ 60 years (mean age: 41.21 ± 15.06 years). Common symptoms were cough (63%), fatigue (34.9%), sore throat (28.2%), and dyspnea (21.8%). Comorbidities included hypertension (23.6%), chronic kidney disease (19%), and diabetes (4.6%). Most cases were mild (68%) or asymptomatic (20.4%), with 10.6% moderate and 1.1% severe (Table 1).

Table 1. *Demographic and Clinical Characteristics*

Characteristic	No. (percentage)
Total	284 (100)
Age	
≤60 years	248 (87.3)
>60 years	36 (12.7)
Age (years) (Mean ± SD)	41.21 ± 15.06
Sex	
Male	89 (31.3)
Female	195 (68.7)
Symptoms	
Cough	179 (63.0)
Fatigue	99 (34.9)
Sore throat	80 (28.2)
Dyspnea	62 (21.8)
Headache	37 (13.0)
Runny nose	26 (9.2)
Loss of smell	25 (8.8)
Nausea	18 (6.3)
Neck pain	16 (5.6)
Diarrhea	14 (4.9)
Abdominal pain	9 (3.2)
Comorbidities	
Hypertension	67 (23.6)
Diabetes	13 (4.6)
Chronic kidney disease	54 (19.0)
Cardiovascular disease	17 (6.0)
Other	16 (5.6)
Severity	
Asymptomatic	58 (20.4)
Mild	193 (68.0)

Moderate	30 (10.6)
Severe	3 (1.1)

Biochemical Marker Levels

Mean urea was 6.39 ± 6.57 mmol/L (range: 1.4 – 36.8 mmol/L), creatinine 211.98 ± 287.08 µmol/L, GOT 32.29 ± 18.97 U/L, and GPT 32.82 ± 27.24 U/L. Elevated urea was observed in 17.6% (50/284) of patients, creatinine in 23.2% (66/284), GOT in 24.6% (70/284), and GPT in 22.2% (63/284) (Table 2).

Table 2. *Biochemical Marker Levels*

Biomarker	Mean ± SD	Min	Max	Normal, No. (%)	Increased No. (%)	Decreased N. (%)
Urea (mmol/L)	6.39 ± 6.57	1.4	36.8	234 (82.4)	50 (17.6)	-
Creatinine (µmol/L)	211.98 ± 287.1	34	32768	211 (74.3)	66 (23.2)	7 (2.5)
GOT (U/L)	32.29 ± 18.97	8	143	214 (75.4)	70 (24.6)	-
GPT (U/L)	32.82 ± 27.24	6	190	221 (77.8)	63 (22.2)	-

Factors Associated with Urea Elevation

Age and Comorbidities

Urea elevation was significantly higher in patients >60 years (34%, 17/50) than ≤60 years (13.3%, 33/248, p = 0.000, Table 3). Urea elevation was associated with hypertension (98% vs. 7.7%, p = 0.000) and cardiovascular disease (28% vs. 1.3%, p = 0.000), but not diabetes (10% vs. 3.4%, p > 0.05, Table 3).

Table 3. *Association of Urea Elevation with Age and Comorbidities*

Category	Urea ≤7.5 mmol/L, No. (percentage)	Urea >7.5 mmol/L, No. (percentage)	Total	p-value
Age				
≤60 years	215 (91.9)	33 (66.0)	248	*0.000*
>60 years	19 (8.1)	17 (34.0)	36	
Comorbidity				
Diabetes				ns
Yes	8 (3.4)	5 (10.0)	13	
No	226 (96.6)	45 (90.0)	271	
Hypertension				*0.000*
Yes	18 (7.7)	49 (98.0)	67	
No	216 (92.3)	1 (2.0)	217	
Cardiovascular Disease				*0.000*
Yes	3 (1.3)	14 (28.0)	17	
No	231 (98.7)	36 (72.0)	267	
Total	234 (100)	50 (100)	284	

ns: not significant

Disease Severity

Urea elevation was associated with disease severity (p = 0.001), absent in asymptomatic cases but present in 33.3% of severe cases (Table 4).

Table 4. *Association of Urea Elevation with Disease Severity*

Severity	Urea ≤7.5 mmol/L No. (percentage)	Urea >7.5 mmol/L No. (percentage)	Total No.	p-value
Asymptomatic	58 (24.8)	0 (0.0)	58	0.001
Mild	153 (65.4)	40 (80.0)	193	
Moderate	21 (9.0)	9 (18.0)	30	
Severe	2 (0.9)	1 (2.0)	3	
Total	234 (100)	50 (100)	284	

DISCUSSIONS

This study identified a 17.6% prevalence of elevated serum urea (>7.5 mmol/L) in COVID-19 patients at Da Nang Pulmonary Hospital, with significant associations with age >60 years, hypertension, cardiovascular disease, and disease severity. The high prevalence of D-dimer elevation (73.2%, as reported in the original study) underscores the interplay between renal dysfunction and coagulopathy. Mean biochemical markers (urea, creatinine, GOT, GPT) were largely within normal ranges, suggesting compensated organ function in most patients. These findings align with global literature while offering insights into Vietnam's regional context, with implications for clinical management and future research.

Prevalence and Pathophysiology of Urea Elevation

The 17.6% prevalence of elevated urea is lower than reported in international studies, such as Gabarre et al. (2020), who found a 27% incidence of AKI (often marked by urea elevation) in ICU COVID-19 patients [12]. This difference may reflect our cohort's predominantly mild-to-moderate cases (88.4%) and younger age (mean: 41.21 years), as severe disease and older age are linked to higher AKI rates [13]. Mean urea (6.39 mmol/L) aligns with Wang et al. (2020), who reported normal urea in non-ICU patients [14], suggesting minimal renal impairment in early-stage disease.

Urea elevation in COVID-19 likely results from multiple mechanisms: (1) prerenal azotemia due to dehydration or hypoperfusion from fever and hypoxia; (2) intrinsic AKI from direct SARS-CoV-2 infection of renal tubular cells via ACE2 receptors; and (3) systemic inflammation (cytokine storm) causing microvascular injury [15]. Su et al. (2020) identified viral particles in renal tubules of COVID-19 autopsy cases, supporting direct viral damage [16]. The wide urea range (1.4–36.8 mmol/L) in our study indicates heterogeneity in renal involvement, from mild dehydration to severe AKI, necessitating tailored monitoring.

Elevated creatinine (23.2%), GOT (24.6%), and GPT (22.2%) suggest multi-organ involvement, consistent with Xu et al. (2020), who reported liver and kidney dysfunction in 20–30% of severe cases [17]. The interplay between renal and hepatic markers may reflect shared inflammatory pathways, such as IL-6-driven endothelial damage [18]. The high D-dimer elevation rate (73.2%) aligns

with Yao et al. (2020), who found elevated D-dimer in 68.4% of severe cases, indicating a hypercoagulable state [19]. Microthrombi in renal vasculature, as described by Batlle et al. (2020), may exacerbate AKI, linking coagulopathy and urea elevation [20].

Age and Comorbidity Associations

The strong association between urea elevation and age >60 years ($p = 0.000$) corroborates Pei et al. (2020), who reported a 3.2-fold higher AKI risk in elderly COVID-19 patients [21]. Older age reduces renal reserve and increases susceptibility to hypoperfusion and inflammation, amplifying urea elevation [22]. Hypertension ($p = 0.000$) and cardiovascular disease ($p = 0.000$) were also associated, aligning with Grasselli et al. (2020), who found that 49% of hypertensive COVID-19 patients developed AKI [23]. Chronic vascular damage in these conditions impairs renal perfusion, while COVID-19's angiotensin II dysregulation exacerbates hypertension-related injury [24].

The lack of association with diabetes ($p > 0.05$) contrasts with Lim et al. (2021), who reported a 2.5-fold AKI risk in diabetic patients [25]. Our cohort's low diabetes prevalence (4.6%) may have limited statistical power, or early glycemic control in hospitalized patients may have mitigated renal impact. Chronic kidney disease (19% prevalence) was not analyzed for association, but its presence likely contributed to urea elevation, as noted by Hirsch et al. (2020) [26].

Disease Severity and Prognostic Value

Urea elevation's association with disease severity ($p = 0.001$), absent in asymptomatic cases but present in 33.3% of severe cases, supports Liu et al. (2020), who linked urea to ARDS and mortality [27]. Urea's prognostic utility may stem from its reflection of systemic inflammation, renal hypoperfusion, and catabolic states in critical illness [28]. The small number of severe cases (n=3) limits definitive conclusions, but the trend aligns with global data, suggesting urea as a marker of disease progression.

D-dimer's high prevalence (73.2%) and prognostic significance, as reported in the original study (>638 µg/L, AUC 0.900), align with Berger et al. (2020), who identified D-dimer >1000 µg/L as a predictor of thrombotic events [29]. The synergy between urea and D-dimer elevation points to a shared pathophysiology involving endothelial dysfunction, microthrombosis, and organ ischemia [30]. In Vietnam, where severe cases were less common due to early containment [31], integrating these markers could prioritize critical care allocation.

Clinical Implications in Vietnam

Vietnam's effective COVID-19 response, including rapid testing and isolation in Da Nang city, reduced severe cases [32]. However, the 17.6% urea elevation rate underscores the need for routine renal monitoring, particularly in older patients and those with hypertension or cardiovascular disease. Cost-effective tests like urea are ideal for resource-limited settings, as highlighted by Nguyen et al. (2021) [33]. Combining urea and D-dimer monitoring could improve risk stratification, as proposed by Rostami et al. (2021), who advocated multi-marker panels for COVID-19 prognosis [34]. In Vietnam, where ICU capacity was strained during outbreaks [35], such strategies could optimize resource use. Future guidelines should incorporate age- and comorbidity-specific thresholds for urea to guide interventions like fluid management or anticoagulation.

The study's findings suggest several research avenues: (1) longitudinal studies to track urea and D-dimer changes post-treatment; (2)

inclusion of additional biomarkers (e.g., cystatin C, NGAL) to assess AKI severity; (3) exploration of genetic or environmental factors influencing renal susceptibility in Vietnamese patients; and (4) validation of urea/D-dimer cutoffs in larger cohorts. Investigating the role of microthrombi in renal injury, as suggested by Santoriello et al. (2020) [36], could clarify pathophysiological links.

This study remained several limitation. The retrospective, single-center design limits generalizability. The small severe case cohort (n=3) reduced statistical power for severity associations. Lack of longitudinal data restricts insights into urea dynamics or treatment effects. D-dimer analysis was limited due to the focus on urea, and other markers (e.g., fibrinogen, IL-6) were not assessed. Selection bias from hospitalized patients may overestimate biochemical abnormalities.

CONCLUSIONS

In conclusion, vlevated serum urea occurred in 17.6% of COVID-19 patients at Da Nang Pulmonary Hospital, associated with age >60 years, hypertension, cardiovascular disease, and disease severity. The high D-dimer elevation rate (73.2%) highlights coagulopathy's role. Routine monitoring of urea, alongside D-dimer, could enhance risk stratification and guide management in Vietnam's resource-constrained healthcare system, particularly for high-risk groups.

Supplementary Materials

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Author Contributions

Study concept: TTL; data acquisition: NTN, NTT; analysis: NTN; drafting: NTT, NTN; statistics: NTN, manuscript revising: TTL.

Institutional Review Board Statement

The study adhered to the Declaration of Helsinki and was approved by the Biomedical Ethics Committee of Da Nang University of Medical Technology and Pharmacy (No. 2021-09/BB-HĐĐĐ, August 10, 2021).

Informed Consent Statement

Consent was waived due to the retrospective use of anonymized records.

Data Availability Statement

Data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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