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Ferritin and procalcitonin in COVID-19 associated acute kidney injury – gender disparities, but similar outcomes

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ABSTRACT

Background: Acute kidney injury is a severe complication of COVID-19. Both COVID-19 and related acute kidney injury are reported in the literature to be more prevalent and more severe in males.

Methods: We performed a retrospective analysis of the COVID-19 associated acute kidney injury cases in order to search for differences between genders regarding patients' and renal outcome.

Results: 250 patients with acute kidney injury were included in the study: 93 women (37.20%), 157 men (62.80%). There were no differences between sexes regarding age. Diabetes mellitus was significantly more present in women. Peak ferritin and procalcitonin levels were significantly higher in men, but other severity markers for COVID-19 did not differ between genders. There were no differences between sexes regarding history of chronic kidney disease, timing of acute kidney injury, need for dialysis or recovery of renal function. ICU admission and in-hospital mortality were similar between men and women.

Conclusions: In our study, COVID-19 related-AKI was more prevalent in men than in women, but the patients' and renal outcome were similar. Significantly higher ferritin and procalcitonin serum levels registered in male patients when compared to women may have additional explanations beside more severe SARS-CoV-2 infection in males.

Keywords: acute kidney injury, gender, procalcitonin, ferritin, COVID-19

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INTRODUCTION

In august 2022, COVID-19 pandemic was reported to have been affected more than 600 million persons and about 6.6 millions have died [1]. Since its arising in 2019, COVID-19 pandemic proved to be a primary respiratory disease with involvement of multiple other organs [2,3]. Acute kidney injury (AKI) represents a severe complication of COVID-19, its incidence varying between 0.5% -67%, depending on meta-analysis performed or the period analyzed [4,5].

Both patient-related and COVID-19-related factors influence the occurrence and evolution of AKI [5]. Among these factors, male gender is reported in most studies to be associated with higher risk for both SARS-CoV-2 infection and COVID-19-related AKI [6]. There are also proofs that COVID-19 and related AKI have more severe outcomes in men than in women, with higher admission to ICU, higher rate of death, higher need for renal replacement therapy, etc [6-10]. SARS-CoV-2 enters into the host's cells by binding its glycoprotein spikes with the cellular receptors ACE2 (angiotensin converting enzyme 2), then proteolytic priming by TMPRSS2 (transmembrane protease serine 2) takes place [11]. ACE2 receptors are expressed in the kidneys, especially in proximal tubular epithelial cells and podocytes [12]. There are proofs that androgen hormones induce an over-expression of both ACE2 and TMPRSS2 [13], while estrogens reduce ACE2 and TMPRSS2 mRNA levels [14,15], providing an explanation for the increased risk for COVID-19 in male gender. Also, Wenzhong Liu and Hualan Li demonstrated that coronavirus proteins attack heme on the 1-beta chain of hemoglobin and this attack will lead to less hemoglobin to carry oxygen and carbon dioxide; due to impossibility to exchange oxygen and carbon dioxid, the lung cells suffer severe inflammation and ultimately the ground-glass pneumonia develops [16]. According to the same authors, the higher the hemoglobin content, the higher the risk of disease [16]. As men have higher hemoglobin than women, they carry a higher risk for developing more severe forms of COVID-19. Moreover, according to various studies men have higher incidence of diabetes mellitus, hypertension or cardiac failure, comorbidities related to a more severe course of COVID-19.

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In view of these data, we performed a retrospective analysis of the COVID-19 associated AKI cases in order to search for differences between genders regarding the patients' and renal outcome.

MATERIALS AND METHODS

We conducted a retrospective analysis on adult patients (>18 years) hospitalized with COVID-19-related AKI during a period of 6 months (1st of November 2020-30th of April 2021) in the Emergency Clinical Hospital "Sf. Ioan" Bucharest, Romania. In this period, our multidisciplinary hospital, equipped with a full-service ICU and a nephrology department with 24/7 availability of renal replacement therapy, was designated by the authorities for the admission of only COVID-19 patients.

Diagnosis and staging of AKI were established on the serum creatinine criterion of the Kidney Disease Improving Global Outcomes (KDIGO) foundation [17]. Both AKI on previously known normal kidneys and acute-on-chronic kidney disease cases were included. AKI was classified as admission-AKI (A-AKI) when it was present at the moment of admission or hospital acquired-AKI (HA-AKI) when it arose during hospitalization. All patients admitted in hospital were confirmed to have SARS-CoV-2 infection with RT-PCR testing. AKI cases secondary to obstruction of urinary tract (postrenal AKI) were excluded.

After inclusion, the following data were collected separately for men and women and compared thereafter:

- Age;
- Preexistent known comorbidities: diabetes mellitus, systemic hypertension, active neoplasia, coronary artery disease, chronic kidney disease (CKD), chronic hepatic disease;
- Extend of COVID-19 pneumonia quantified by a radiologist in percentages of affected pulmonary parenchyma (PAPP) on chest computer tomography (CT);
- Laboratory markers of COVID-19 severity: C-reactive protein, interleukin-6 (IL-6), ferritin, procalcitonin, D-dimers, neutrophils/lymphocytes ratio. Peak values during hospitalization were used in the analysis, except for lymphocyte count where lowest values were used;
- Characteristics of AKI: KDIGO stages, timing (admission-AKI or hospital-acquired AKI), need for dialysis, recovery of renal function in survivors. Recovery of renal function was classified as total when creatinine values returned to normal values in patients with previous normal kidney function or partial when it returned to basal creatinine values in acute-on-chronic kidney disease;
- Type of oxygen supplementation: no need, mask, CPAP (continuous positive airway pressure), mechanical ventilation;
- ICU (intensive care unit) admission;
- Duration of hospitalization in days;
- Death rate.

Data were retrieved from the electronic database of the hospital. Approval for the study was obtained from the Ethics Committee of the Hospital (23985/06.09.2022). Informed consent of the patients was waived do to non-interventional, observational nature of the research. The study was performed in accordance with Good Clinical Practice and ethical standards of Declaration of Helsinki (revised 2014).

All the data from the study were analyzed using IBM SPSS Statistics 25. Quantitative variables were tested for normal distribution using the Shapiro-Wilk Test, were written as averages with standard deviations or medians with interquartile ranges and were compared between genders using Mann-Whitney U tests. Qualitative variables were written as counts or percentages and were compared between genders using Pearson Chi-Square tests. The measures of association between other factors and gender were estimated as odds ratios with 95% confidence intervals (using the contingency tables where the female group was the reference category). Any association where the statistical probability was less than α=0.05 was considered to be significant. AUC-ROC (Area Under the Curve-Receiver Operator Characteristics) curves were used for establishing cut-off values for statistically significant biomarkers in prediction of mortality; the performance of the prediction was estimated using AUC values with 95% confidence intervals and cut-off values were calculated based on the highest Youden index. Predictive accuracy was interpreted as excellent for AUC results over 0.8, good for values between 0.7-0.8, and sufficient for AUC values between 0.6-0.7.

RESULTS

In the mentioned period, a total of 1557 COVID-19 admissions were recorded in our hospital; among them, 938 (60.24%) were male patients.

250 patients were diagnosed with AKI either at admission or during hospitalization and they were included in the study: 93 women (37.20%) and 157 men (62.80%). General characteristics of the AKI patients are presented in Table 1. The majority of the patients was > 65 years and had increased burden of comorbidies. Taking into consideration severe alterations in laboratory markers, the high number of cases needing invasive type of oxygen supplementation, more than 30% of patients admit-

ted to ICU and increased death rate, we classified our patients as moderate and severe form of COVID-19.

Analyzing comparatively the data recorded for men and women, we found that age was not significantly different between genders (median age: 74 years – women, 72 years – men, p=0.243) (Table 2). Most of the analyzed comorbidities were not significantly different as frequencies between genders (p>0.05) with the exception of diabetes mellitus, which was significantly more prevalent in women (49.5% vs. 34.4%; p=0.019).

In regard to laboratory markers of COVID-19, most of them were not significantly different between genders (p>0.05), except for peak ferritin and peak procalcitonin (Table 3), both being significantly higher in men than women (median peak ferritin 1016 ng/mL in women vs. 1535 ng/mL in men, p=0.004; median peak procalcitonin 0.33 ng/mL in women vs. 0.88 ng/mLin men, p=0.003). No difference between men and women was found in the PAPP on CT (Table 3).

Comparing AKI features between genders, we found that neither the timing of AKI (p=0.137), nor the AKI stages (p>0.05) differed significantly between men and women. Also, the need for dialysis (p=0.313) and recovery of renal function in survivors, respectively, were not significantly different between genders (p>0.05) (Table 4).

Moreover, no significant differences between men and women (p>0.05) were revealed regarding the re-

Table 1. General characteristics of all AKI patients

Number of cases	
Total	250 (100%)
Males	157 (62.8%)
Females	93 (37.2%)
Median age (IQR)	73 (64-82.25)
>65 years (No.(%))	179 (71.60%)
Comorbidity	
Preexistent CKD	104 (41.60%)
Neoplasia	53 (21.20%)
Chronic hepatic disease	52 (20.80%)
Coronary artery disease	153 (61.20%)
Diabetes mellitus	100 (40%)
Systemic hypertension	194 (77.60%)
CT scan (number of cases quantified (%))	158 (63.20%)
PAPP on CT scan (median (IQR), %)	50 (20-75)
Laboratory markers COVID-19	
Peak IL-6 (median (IQR), pg/mL)	136 (46-752)
Peak ferritin (median (IQR), ng/mL)	1416.5 (731-2761)
Peak C-reactive protein (median (IQR), mg/dL)	118.49 (68.04-206.59)
Peak procalcitonin (median (IQR), ng/mL)	0.71 (0.21-4)
Peak D-dimer (median (IQR), µg/mL FEU)	2.68 (1.475-8.955)
Neutrophils /lymphocytes ratio (median (IQR))	10.27 (5.17-17.63)

Characteristics of AKI	
KDIGO stages	
KDIGO 1	85 (34%)
KDIGO 2	78 (31.2%)
KDIGO 3	87 (34.8%)
Timing of AKI	
A-AKI	160 (64%)
HA-AKI	90 (36%)
Need for dialysis	22 (8.88%)
Recovery of renal function in survivors (124 cases) – No (%)	
Total	69 (55.64%)
Partial	48 (38.70%)
Absent (HD dependence)	7 (5.64%)
Oxygen requirements (the most severe treatment registered)	
No need	41 (16.4%)
Mask	110 (44%)
CPAP	34 (13.6%)
Mechanical ventilation	65 (26%)
ICU admission	99 (39.60%)
Duration of hospitalization in days (median(IQR))	
In all patients	13 (9-17)
In survivors	14.5 (12-19)
Deceased	126 (50.40%)

Legend: IQR = interquartile range; CKD = chronic kidney disease; CT = computer tomography; PAPP = percentages of affected pulmonary parenchyma (on CT); IL-6 = interleukin-6; FEU = fibrinogen equivalent units; KDIGO = Kidney Disease Improving Global Outcomes; A-AKI = admission AKI; HA-AKI = hospital-acquired AKI; HD = hemodialysis; CPAP = continuous positive airway pressure; ICU = intensive care unit.

Table 2. Comparison of age and comorbidities between genders

	Women	**Men**	**p**
Number of cases (% from total of 250 patients)	93 (37.20%)	157 (62.80%)	-
Median age (IQR)	74 (66-84.5)	72 (64-82)	0.243*
Diabetes mellitus- No/%	46/49.5	54/34.4	0.019**
Neoplasia- No/%	20/21.5	33/21.2	0.948**
Coronary artery disease- No/%	57/61.3	96/61.1	0.982**
Systemic hypertension- No/%	68/73.1	126/80.3	0.191**
Chronic kidney disease- No/%	34/36.6	70/44.6	0.213**
Chronic hepatic disease- No/%	14/15.1	38/24.2	0.085**

*Mann-Whitney U Test, **Pearson Chi-Square Test, IQR = interquartile range

Table 3. Comparison of markers of COVID-19 between men and women

	Women	Men	p
CT scan – number of cases cuantified/ (/%)	59/63.4	99/63.1	-
CT scan- PAPP (median (IQR), %)	50 (15-75)	50 (25-75)	0.306*
Peak IL-6 (median (IQR), pg/mL)	90.87 (24.3-515.2)	143.7 (49.4-697.3)	0.084*
Peak ferritin (median (IQR), ng/mL)	1016 (616.4-2164)	1535 (902.3-3143)	0.004*
Peak C-reactive protein (median (IQR), mg/dL)	107.7 (50.7-206.7)	121 (77.3-209.6)	0.154*
Peak procalcitonin (median (IQR), ng/mL)	0.33 (0.14-2.18)	0.88 (0.25-5.23)	0.003*
Peak D-dimer (median (IQR), µg/mL FEU)	2.485 (1.1-6.05)	3.04 (1.59-10.16)	0.139*
Lymphocytes count (median (IQR), 10^3 cells/mmc)	0.84 (0.575-1.215)	0.69 (0.475-1.02)	0.025*
Neutrophils /lymphocytes ratio (median (IQR))	9.458 (5.236-16.394)	10.857 (5.137-19.619)	0.528*

*Mann-Whitney U Test; CT= computer tomography; PAPP = percentages of affected pulmonary parenchyma (on CT); IQR = interquartile range; IL-6 = interleukin-6; FEU = fibrinogen equivalent units.

Table 4. AKI features in men and women

	Women	Men	p	OR (95% C.I.)
KDIGO stages –No/%				
KDIGO 1	34/36.55	51/32.48	p= 0.511**	0.835 (0.487-1.430)
KDIGO 2	32/34.40	46/29.29	p=0.399**	0.790 (0.456-1.367)
KDIGO 3	27/29.03	60/38.21	p=0.141**	1.512(0.871-2.625)
Timing of AKI - No/%				
Admission-AKI	56/60.2	109/69.4	0.137**	0.667 (0.390-1.140)
Hospital acquired AKI	37/39.8	48/30.6		
Need for dialysis- No/%	6/6.5	16/10.2	0.313**	1.645 (0.620-4.365)
Recovery of renal function in survivors				
Total – No/%	27/55.1	42/56.0	0.922**	0.893 (0.505-1.579)
Partial – No/%	20/40.8	28/37.3	0.697**	0.792 (0.417-1.505)
Absent (HD-dependence)- No/%	2/4.1	5/6.7	0.542**	1.497 (0.285-7.874)

**Pearson Chi-Square Test; KDIGO = Kidney Disease Improving Global Outcomes; OR = odd ratio; C.I. = confidence interval; HD = hemodialysis.

maining of analyzed data either: need for oxygen supplementation, admission to ICU, duration of hospitalization or death rate (Table 5).

An AUC-ROC analysis was performed for prediction of mortality using peak ferritin and procalcitonin. The results are presented in Table 6 and Figure 1. Both markers had at least sufficient accuracy for prediction. Cut-off values were significantly different between genders. In women, the cut-off value of peak ferritin calculated for the highest value of the Youden index (0.356) was 1416.5 ng/mL with a sensitivity of 59% and a specificity of 76.6%; in men, the cut-off value was 2574.5 ng/mL with a sensitivity of 55.3% and a specificity of 90.6% (highest Youden index 0.459). Regarding procalcitonin, in women, the cut-off value was 0.58 ng/mL with a sensitivity of 69.2% and a specificity of 85.1% (highest Youden index 0.543) and in men it was 1.00 ng/mL, having a 68.4% sensitivity and 82.2% specificity (highest Youden index 0.497).

DISCUSSION

Comparing COVID-19 related AKI between genders in a period of 6 months, we found a higher incidence of AKI in men than in women. We also observed that, among all patients admitted in the same period with COVID-19, male gender prevailed. These observations are in ac-

Table 5. Comparisson of analyzed parameters between genders

	Women	Men	p	OR (95% C.I.)
Oxygen requirements (the most severe treatment registered)- No/%				
No need	14/15.05	27/17.19	p=0.658**	1.172 (0.580-2.368)
Mask	48/51.61	62/39.49	p=0.062**	0.612 (0.365-1.027)
CPAP	13/13.97	21/13.37	p=0.893**	0.950 (0.451-2.001)
Mechanical ventilation	18/19.35	47/29.93	p=0.065**	1.780 (0.960-3.301)
ICU admission- No/%	34/36.6	65/41.4	0.449**	1.226 (0.723-2.079)
Duration of hospitalization (days) (median (IQR))				
All patients	13 (9-17.75)	13 (8.5-17)	0.774*	-
Survivors (N=124 / W:49, M:75)	15 (12-18.5)	14 (12-19)	0.601*	-
Deaths- No/%	44/47.3	82/52.2	0.452**	1.218 (0.729-2.035)

*Mann-Whitney U Test, **Pearson Chi-Square Test; OR = odd ratio; C.I. = confidence interval; CPAP = continuous positive airway pressure; ICU = intensive care unit; IQR = interquartile range.

Table 6. Receiver Operating Characteristic (ROC) analysis for prediction of mortality using peak ferritin and calcitonin values

Parameter (peak values)	Cut-off value (ng/mL)	AUC (95% C.I.)	Std. Error	p	Sensitivity %	Specificity %
Ferritin						
Women	1416.5	0.686 (0.571-0.801)	0.059	0.003	59	76.6
Men	2574.5	0.774 (0.697-0.850)	0.039	<0.001	55.3	90.6
Procalcitonin						
Women	0.58	0.816 (0.725-0.907)	0.046	<0.001	69.2	85.1
Men	1.00	0.778 (0.700-0.857)	0.040	<0.001	68.4	82.2

AUC = area under the curve; C.I. = confidence interval.

cordance with the majority of previously published studies and meta-analysis.

Nevertheless, when comparing data regarding AKI type (AKI/ acute-on-chronic-kidney disease), timing (A-AKI/HA-AKI) and severity of AKI (KDIGO stages, need for dialysis, recovery of renal function in survivors, number of deaths), we found no differences between genders. Regarding underlying diseases, we noted higher frequency of diabetes mellitus in women. These results are in contrast with many other studies which reported not only a more severe course of AKI in men, but also a higher prevalence of various comorbidities as CKD, diabetes mellitus or hypertension.

Facing a practically identical course of AKI during hospitalization in both sexes, we tried to search if the primary etiology of AKI – i.e. COVID-19 disease – had also similar features in men and women. As such, we compared between genders the laboratory and radiologic markers of COVID-19 severity. We noted significant higher peak values of ferritin and procalcitonin in men, but there were no differences in the extend of COVID-19 pneumonia assessed on CT, other laboratory markers (C-reactive protein, neutrophils/lymphocytes ratio, D-dimers); also no differences were revealed regarding the oxygen need, ICU admission or mortality. Thereby, we tried to find additional explanations for these sex disparities.

Increased ferritin and procalcitonin serum levels are considered to be directly linked to COVID-19 severity in most reports, although not always together in various studies [18,19].

Elevated serum procalcitonin is used in clinical practice as a diagnostic tool for bacterial infections [20]. Little is known regarding the elimination pathway of procalcitonin, but some authors described that in various degrees of kidney dysfunction, serum levels of procalcitonin increased with 30-50% [21]. Increased serum procalcitonin levels in chronic kidney disease (CKD) without signs of infections have been reported in several studies [22,23] and the authors concluded that a higher cut-off of procalcitonin level must be used in CKD patients in order to diagnose an infection. Likewise, Wu et al, in a case-control study, identified a cut-off value for procalcitonin level three times higher than the reference value in order to differentiate CKD patients from healthy persons [23]. Wu et al concluded also that increased procalcitonin levels in CKD patients is partially due to accumulation of proinflammatory cytokines in CKD, progressively higher as kidney function diminishes, but also due to reduced renal clearance of procalcitonin [19]. Reduced renal clearance of procalcitonin in AKI with abnormal increased serum levels is also discussed and reported in the literature [24,25] and some authors

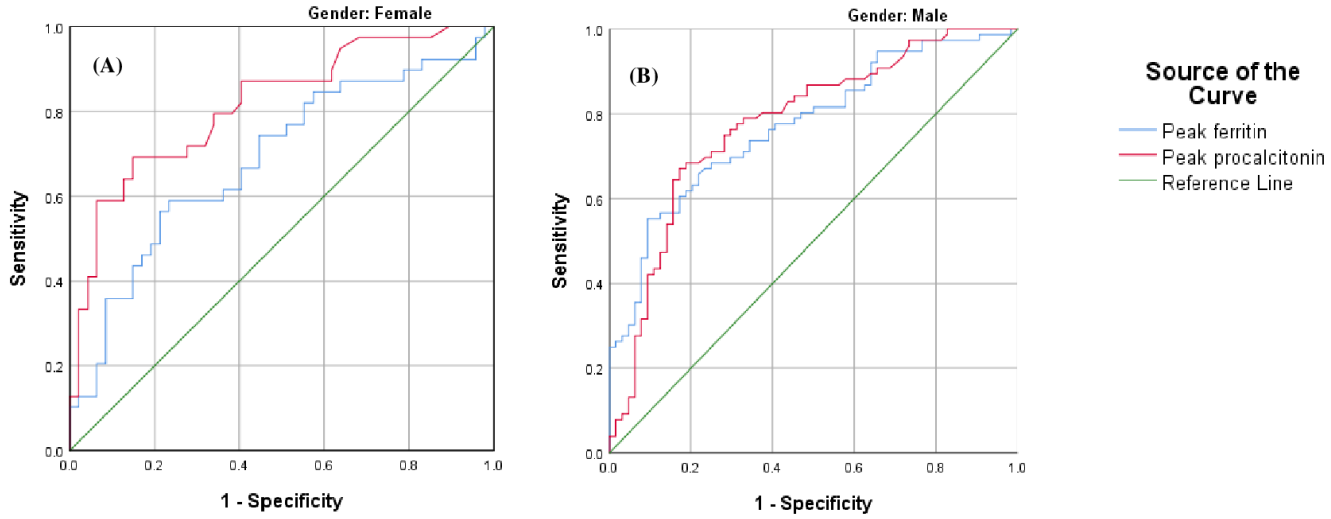

Fig.1. ROC curves for prediction of mortality using peak ferritin and calcitonin values in women (A) and men (B)

warned that a higher cut-off value must be used in AKI patients for diagnosis of infection [26,27]. Nevertheless, in our case of similar course of AKI+COVID-19 in both sexes, we cannot explain why serum procalcitonin was higher in men, though we can speculate that history of chronic hepatic disease found in a higher number of cases in male patients (although not significant) may be involved. In inflammatory conditions, besides other organs, procalcitonin is also synthesized in the liver and it would be expected that, in severe hepatic failure, its production to be reduced [28]; yet, some authors reported that a significant proportion of patients with cirrhosis without bacterial infection exhibits increased serum procalcitonin levels [29]. A limit of our study, relevant for the results regarding procalcitonin, is that we did not register the degree of liver dysfunction, especially because there were cases of COVID-19 with liver involvement and also some hepatic adverse reactions secondary to medication. Also, another limit of our study, we did not collect information regarding use, doses and duration of antimicrobial therapy, information that is difficult to be obtained in a retrospective analysis from the electronic database.

The hyperinflammatory phenotype in COVID-19 evolution is characterized primarily by hypercytokinaemia, with further expression of macrophage activation syndrome characteristics, namely fever, increased levels of CRP and serum ferritin, the latter of these being most likely released from damaged cells, also cytopenias and coagulopathy [30,31]. In addition to the fact that serum ferritin is a well recognized inflammatory marker and has pro-inflammatory effects, some data suggest that ferritin also has a cytoprotective effect by sequestering free iron ions, thus diminishing endothelial apoptosis and oxidative stress [31,32]. There are reports in the literature revealing no influence of increased ferritin on mortality in critical COVID-19 patients [33] or in COVID-19-associated AKI patients [34]. Thus, a possible explanation of similar outcome of AKI in both genders, despite higher ferritin in men in our study, may be the cytoprotective effect of ferritin. Also, it is important to mention that in healthy adults, ferritin has normal range values higher in males than in females and the upper normal limits are significantly different between laboratories. For example, according to medicinenet.com, normal ferritin levels range from 12 to 300 ng/mL for men and 12 to 150 ng/mL for women, and according to webmd.com, normal ferritin levels range from 24 to 336 ng/mL for men and 11 to 307 ng/mL for women. In our laboratory, normal ferritin values range between 13-150 ng/mL for women, and between 30-400 ng/mL for men. The reason for a physiologically higher ferritin in men than in women is due to larger iron stores, possible related to the sex hormone difference. Therefore, regarding our finding (higher ferritin in men), we can speculate that the baseline level from which ferritin started to rise is higher in men and, as a result, the difference between the sexes is not due to a more severe inflammation in men. Finally, other chronic inflammatory diseases more prevalent in men (like hyperuricemia and gout for example [35]) and not registered in the study may have been contributed to this discrepancy.

In a study performed by Raimondi et al, mortality was also not different between genders in the case of severe COVID-19, although men were more affected than women by the disease [36]. Taking into consideration that the severity of COVID-19 in all our patients was high – as illustrated in Table 1, we may presume that the higher ferritin and procalcitonin levels in men were indeed within the context of more severe disease than in women and, similarly to Raimondi's results, the outcomes did not differ. It is to mention that in Raimondi's study group, no comparison between AKI and non-AKI patients outcome was performed [36].

CONCLUSIONS

In our study, COVID-19 associated-AKI was more prevalent in men than in women, but the patients' and renal outcome were similar. Significantly higher ferritin and procalcitonin serum levels were noted in male patients when compared to women, in the absence of other COVID-19 severity markers differences and these results may have additional explanations besides more severe SARS-CoV-2 infection in males.

AUTHOR CONTRIBUTIONS

Conceptualization: RD; methodology: RD, DC, CE; software: CE, OSD; validation, RD, DC, CE, VIA; formal analysis: RD, OSD; investigation: RD, DC, CE, TFL, FLF, OSD, VIA; data curation, RD, CE, TFL, FLF, OSD, VIA; writing-original draft preparation: RD; writing-review and editing: RD, DC, CE, TFL, FLF, OSD, VIA; visualization: RD, CE; supervision: RD.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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