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CLINICAL IMPACT OF ELEVATED HIGH-SENSITIVITY TROPONIN I LEVELS IN COVID-19 HOSPITALIZATIONS

IMPACTO CLÍNICO DOS NÍVEIS ELEVADOS DE TROPONINA I DE ALTA SENSIBILIDADE NAS HOSPITALIZAÇÕES POR COVID-19

IMPACTO CLÍNICO DE LOS NIVELES ELEVADOS DE TROPONINA I DE ALTA SENSIBILIDAD EN HOSPITALIZACIONES POR COVID-19

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ABSTRACT: Objective Troponin I (TnI) is a biochemical marker of high specificity and sensitivity in myocardial injuries according to the 99th percentile values. The elevated serum levels of such proteins were recently described in the infection by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The study aimed to relate the changes in Troponin I concentrations to the presence of comorbidities, clinical evolution, and prognosis of patients affected and hospitalized for covid-19 attended at a tertiary hospital in Western Paraná State. **Material and Methods** This is a cross-sectional and retrospective study based on the collection of electronic data from patients hospitalized with covid-19 with alterations in the high-sensitivity troponin I (hsTnI) dosage. The correlation between clinical profiles and disease evolution was carried out through descriptive and statistical analyses. **Results** Among 718 patients, 366 presented an increase in hsTnI. The patients were predominantly elderly over 65 years old and male. The dosage presented a higher mean for patients who were discharged compared to patients who died (p-value <0.0001). However, the predominant outcome was death (52.19%). Higher troponin I values obtained here are of multifactorial origin and are significantly related to hypertension and kidney disease. The overall mean of hsTnI measured was 1601.55 ng/L. **Conclusion** Cardiac injury associated with SARS-CoV-2 infection was evidenced through high-sensitivity Troponin I dosage in hospitalized patients with covid-19 who died.
DESCRIPTORS: Cardiac injury. hsTnI. SARS-CoV-2. Hospitalization.

RESUMO: Introdução: A Troponina I (TnI) é um marcador bioquímico de alta especificidade e sensibilidade para lesões miocárdicas, com base no percentil 99. Os níveis elevados de troponina foram observados na infecção por SARS-CoV-2 (covid-19). O estudo teve como objetivo relacionar as alterações nas concentrações de Troponina I com a presença de comorbidades, evolução clínica e

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prognóstico de pacientes acometidos e hospitalizados por covid-19 atendidos em um hospital terciário do Oeste do Estado do Paraná. **Métodos:** Estudo retrospectivo e transversal, com coleta de dados eletrônicos de pacientes hospitalizados com covid-19 e alterações nos níveis de troponina I. A análise estatística correlacionou os perfis clínicos com a evolução da doença. **Resultados:** Entre 718 pacientes, 366 apresentaram aumento nos níveis de Troponina I de Alta Sensibilidade (hsTnI). A maioria dos pacientes eram pessoas idosas (acima de 65 anos) e do sexo masculino. A dosagem foi mais alta nos pacientes que receberam alta comparados aos que faleceram ($p < 0,0001$). O principal desfecho foi o óbito (52,19%). Os níveis elevados de troponina I estão relacionados a fatores como hipertensão e doenças renais. A média geral de hsTnI foi 1601,55 ng/L. **Conclusão:** Lesões cardíacas associadas à infecção por SARS-CoV-2 foram evidenciadas pela dosagem de troponina I em pacientes hospitalizados com covid-19 que faleceram.
DESCRITORES: Lesão cardíaca. hsTnI. SARS-CoV-2. Hospitalização.

RESUMEN: Introducción: La Troponina I (TnI) es un marcador bioquímico específico y sensible para lesiones miocárdicas, según el percentil 99. Los niveles elevados de troponina se han observado en la infección por SARS-CoV-2 (covid-19). El estudio tuvo como objetivo relacionar los cambios en las concentraciones de Troponina I con la presencia de comorbilidades, evolución clínica y pronóstico de pacientes afectados y hospitalizados por covid-19 atendidos en un hospital terciario del estado de Paraná. **Métodos:** Estudio retrospectivo y transversal basado en la recolección de datos electrónicos de pacientes hospitalizados con covid-19 y alteraciones en los niveles de troponina I. Se realizó un análisis estadístico para correlacionar los perfiles clínicos con la evolución de la enfermedad. **Resultados:** De 718 pacientes, 366 presentaron aumento en los niveles de Troponina I de Alta Sensibilidad (hsTnI). La mayoría era de personas mayores (más de 65 años) y de sexo masculino. Los niveles de troponina fueron más altos en los pacientes dados de alta en comparación con los fallecidos ($p < 0.0001$). El principal desenlace fue el fallecimiento (52,19%). Los niveles elevados de troponina I están relacionados con la hipertensión y enfermedades renales. La media general de hsTnI fue de 1601,55 ng/L. **Conclusión:** Las lesiones cardíacas asociadas con la infección por SARS-CoV-2 se evidenciaron mediante la dosificación de troponina I en pacientes hospitalizados con covid-19 que fallecieron.
DESCRIPTORES: Lesión cardíaca. hsTnI. SARS-CoV-2. Hospitalización.

INTRODUCTION

Cardiac troponins I and T isoforms are biochemical markers of high sensitivity and specificity when measured in myocardial injuries. Such regulatory proteins of muscle contraction are released into the bloodstream within hours after cell damage to cardiomyocytes. Serum troponin concentrations remain at peak levels in the circulation for days after the event, which provides indications for clinical diagnosis and prognosis [1-3].

Troponins can be detected at levels without clinical significance in healthy people, while elevated dosages characterize cardiac injury. Through discriminatory indices established by the 99th percentile, threshold values used as a reference for the accuracy of laboratory tests and biochemical analysis of troponins are defined[4,5]. The elevation of these markers is described in pathologies such as sepsis, myocardial diseases (Heart Failure, heart attacks, and others), stroke, Chronic Obstructive Pulmonary Disease (COPD), pneumonia, and, recently, in the Severe Acute Respiratory Syndrome Coronavirus-2 disease (SARS-CoV-2)[4,6].

The 2019 global pandemic caused by SARS-CoV-2, an RNA virus of the Coronaviridae family, has posed a public health challenge regarding the clinical course and consequences of the disease, covid-19[6,7]. The clinical presentation of the disease is characterized by respiratory symptoms, myalgias, coughing, and respiratory failure. More serious complications of hospital morbidity and mortality may occur mainly in the risk group, consisting of elderly people and patients with comorbidities such as arterial

hypertension, diabetes mellitus, obesity, and heart diseases[8,9].

The association between cardiac injuries and SARS-CoV-2 infection occurs through different mechanisms. The binding of the virus spike protein to the Angiotensin II-converting enzyme (ACE 2) leads to negative modulation of enzymes with antioxidant action, expressed in the heart and lungs, with consequent alteration in the Renin-Angiotensin-Aldosterone System (RAAS)[10,11]. The physiopathology of damage to myocytes involves endothelial dysfunction, increased oxidative stress, hypoxemia, imbalance between oxygen supply and demand, and direct injury caused by the virus[12,13].

The clinical profile of systemic inflammation is due to the increased expression of cytokines and the progression of the disease that causes myocyte injury and consequent elevation of the main inflammatory biochemical markers, such as C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), Creatine phosphokinase (CPK), Creatine phosphokinase-MB (CPK-MB), troponins, and hematological and renal indicators. The aggravating risk factors and cardiovascular complications worsen the body's response to the disease caused by the virus, resulting in shock, multiple organ failure, and even death[13,14].

It is important to highlight that the values obtained in biochemical dosages of Troponin can be decisive for medical treatment and prognosis related to covid-19. Bearing this in mind, the study aimed to relate the changes in Troponin I concentrations to the presence of comorbidities, clinical evolution, and prognosis of patients affected and hospitalized for covid-19 attended at a tertiary hospital in Western Paraná State.

MATERIAL AND METHODS

The present study was cross-sectional and retrospective and was approved by the Ethics in Human Research Committee (CAAE) under opinion number 54047421.9.0000.0107. The study included patients of the Western Paraná University Hospital - HUOP hospitalized in Intensive Care Units (ICU) and infirmaries, with confirmation of covid-19 infection through the laboratory methods of Real-Time Reverse-Transcription Polymerase Chain Reaction (RT-PCR), Rapid Molecular Test (ID NOW ™ - Abbott ®), and Rapid Antigen Detection Tests, obtained via electronic medical records of the Philips Tasy ® System.

Regarding the laboratory methods used, according to the World Health Organization (WHO), the Real-Time Reverse-Transcription Polymerase Chain Reaction (RT-PCR) is the "gold standard" for the diagnosis of covid-19. In this method, viral genetic material (RNA) is extracted from a sample and amplified until detected. In turn, the ID NOW™ Rapid Molecular Test is of similar qualitative methodology, but it is used for faster and more urgent results, such as in hospital cases. Rapid diagnostic tests (RDTs) for SARS-CoV-2 antigens were performed using the qualitative method. The samples were obtained through nasopharyngeal aspirate collected by swab before or at the time of hospitalization.

After the positive result, individual data were listed for analysis, such as age, sex, comorbidities, outcome, and biochemical markers performed. Only the results obtained on the day of patient admission regarding the serum levels of Ultra-sensitive Troponin I (hsTnI), creatinine (CREA), and urea (UREA) were analyzed. The comorbidities considered for the study were: Cardiovascular Diseases (CVD), Obesity, Hypertension, Diabetes, and Kidney Diseases (Acute or Chronic Renal Failure). The data were organized in tables in Excel®.

Troponin I dosages were performed using the automated Enzyme Linked Fluorescent Assay (ELFA) method in the Mini-VIDAS ™ multiparameter equipment in the clinical analysis laboratory of the Western Paraná University Hospital - HUOP.

The results were evaluated according to the values established by the 99th percentile and quantified in ng/L. After the biochemical analysis, results above 11 ng/L for women and 25 ng/L for men were considered elevated, with an overall mean of 19 ng/L[2].

In addition to the patients' medical records regarding the presence or absence of acute or chronic renal failure, the patients' renal function was monitored and evaluated through creatinine and urea measurements (mg/dL). Quantitative dosing of the concentration of these analytes in serum was carried out using the VITROS® 4600 Chemistry System by QuidelOrtho. The estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[15].

The correlation among clinical histories, disease evolution, and values such as Troponin levels and age was performed by descriptive statistical analysis with means and standard deviations. Using R® Programming, the absolute frequency of each variable was calculated, and the dependence among the outcome and the variables sex, age, and comorbidities was analyzed using the Chi-square test (x^2 =p-value <0.05)[16].

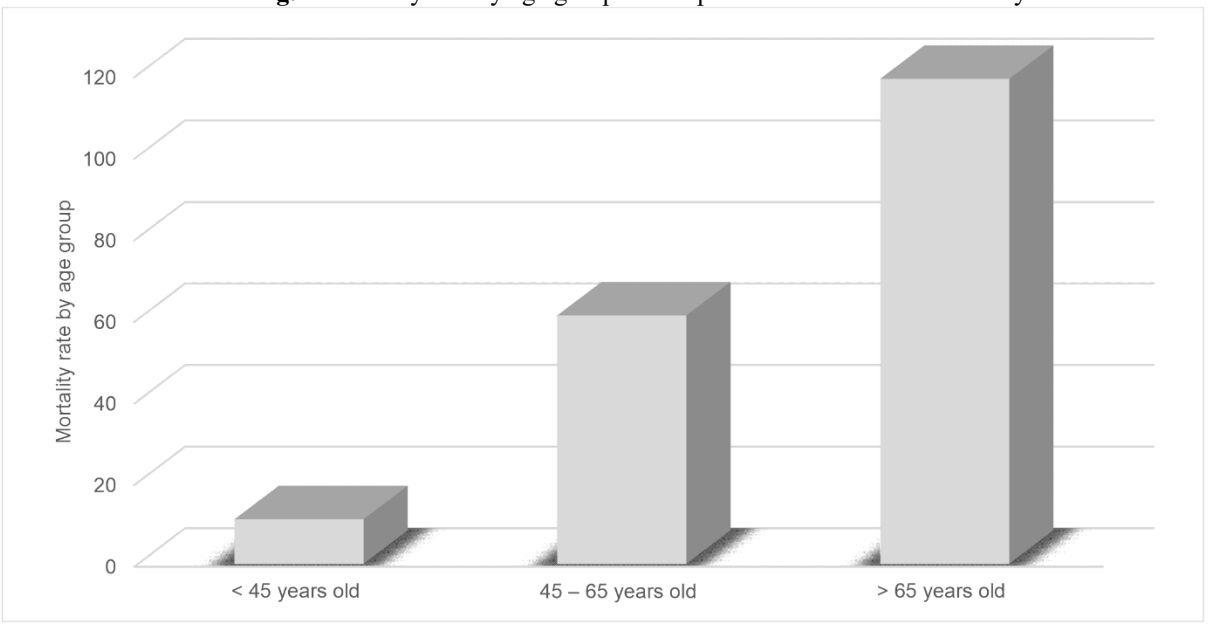
The quantitative variable, high-sensitivity Troponin I, was assessed for normality using histograms and the Shapiro-Wilk test. The Mann-Whitney test was used to evaluate the Troponin I concentration in relation to qualitative variables of three categories: sex, comorbidities, and outcome. When there were three age groups determined, the Kruskal-Wallis test was used. Statistical tests were considered significant if the p-value was <0.05.

RESULTS

From April 2020 to April 2021, 781 patients with covid-19 were admitted to the ICUs and infirmaries of the hospital in which this study was carried out. Given the 99th percentile, the increase in the reference values of high-sensitivity Troponin I occurred in 366 (46.86%) patients who were assigned to the analysis of other variables.

Regarding the sex of the patients, 202 (55.19%) were male, and 164 (44.81%) were female. The age group was sorted into three categories of patients, of which <45 years old accounted for 40 patients (10.93%), 45 to 65 years old for 147 patients (40.16%), and >65 years old accounted for 179 patients (48.91%). Among the 366 patients evaluated, 191 (52.19%) died, while the remaining patients were discharged from the hospital. The mortality rate by age group in hospitalizations is represented in Fig. 1.

Fig. 1 Mortality rate by age groups in hospitalizations found in the study.



Regarding the patients' most frequent comorbidities, 234 (63.93%) had hypertension, 113 (30.87%) diabetes, 73 (19.35%) obesity, 63 (17.21%) cardiovascular diseases (CVD), and 33 (9.02%) kidney diseases (acute or chronic renal failure), as presented in Table 1. For these results, the association between one or more comorbidities

per individual was considered in 174 patients, for example, the association between hypertension and diabetes or among hypertension, cardiovascular disease, and kidney disease in the same patient.

Table 1 Absolute frequency of the characteristics of the evaluated COVID-19 patients.

		Outcome		x^2 observed	p-value
		Discharge (n=175)	Death (n=191)		
Sex	Female (n=164)	84	80	1,381	0,24
	Male (n=202)	91	111		
Age	< 45 years old (n=40)	29	11		
	45 to 65 years (n=147)	86	61	31,159	<0,0001
	> 65 years old (n=179)	60	119		
Comorbidities	Hypertension (n=234)	111	123	0,037	0,847
	Diabetes (n=113)	45	68	4,18	0,041
	Obesity (n=73)	47	26	10,033	0,002
	CVD (n=63)	23	40	3,899	0,048
	Kidney diseases (n=33)	15	18	0,081	0,776

Still, according to Table 1, and regarding comorbidities associated with outcome, among patients with obesity, 35.62% died (p-value = 0.002), patients with diabetes, 52.19% died (p-value = 0.041), and out of those with cardiovascular diseases, 63.49% died (p-value = 0.048). Kidney diseases (p-value = 0.776) and hypertension (p-value = 0.847) were not related to patients' deaths, only when compared to the elevation of troponin levels.

The Troponin I mean obtained for female patients was 770.46 ng/L, and for males was 2276.06 ng/L, but without statistical difference. The overall mean of the Troponin I value was 1601.55 ng/L, as presented in Table 2.

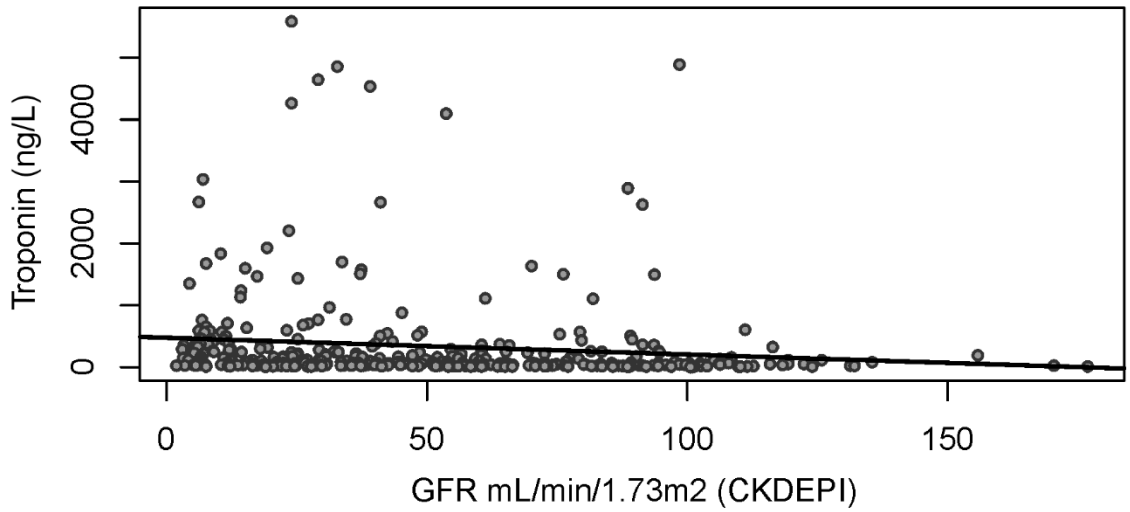
Table 2 Analysis of Troponin I concentration in relation to other variables in COVID-19 patients.

		Troponin I ng/L (1601,6 ± 12662,1)	p-value
Sex	Female (n=164)	762,86 ± 3034,46	0,08[1]
	Male (n=202)	2276,06 ± 16812,42	
Age	< 45 years old (n=40)	881,87 ± 426653	0,5481[2]
	45 to 65 years old (n = 147)	2830,63 ± 19575,40	
	> 65 years old (n = 179)	751,29 ± 2895,06	
Outcome	Discharge (n=175)	2241701 ± 17944,61	< 0,0001[1]
	Death (n=191)	1013,40 ± 3519,35	
Comorbidities	Hypertension (n = 234)	1310,47 ± 8814,15	0,04[1]
	Diabetes (n = 113)	1968,96 ± 12327	0,04[1]
	Obesity (n = 73)	348,42 ± 648,60	0,5[1]
	CVD (n = 63)	758,63 ± 2945,22	0,417[1]
	Kidney disease (n = 33)	4204,36 ± 22242,87	0,732[1]

Among the evaluated factors that presented statistical differences, Troponin I displayed a higher mean for patients discharged from hospital than those who died (p-value < 0.0001). In addition, it displayed means above the 99th percentile due to hypertension (p-value = 0.04) and diabetes (p-value = 0.04). Regarding the evaluated comorbidities, kidney diseases had the highest mean of Troponin I concentration (42,204.34

ng/L). Renal function was assessed by eGFR, with a mean of 49.52±35.11 mL/min/1.73m^2. The correlation between patients' Troponin and eGFR was significantly negative (Fig. 2), indicating dependence of 28.29% (p-value 3.67x10-8, R^2 -0.28).

Fig. 2 Correlation between Troponin variation (ng/L) and eGFR (mL/min/1.73m^2).



DISCUSSION

According to the description of Atallah et al. [17], biomarkers of cardiac injury are notably involved in the diagnosis, monitoring, and prognosis of the covid-19 patient. The increase in Troponins is related to negative modulation of ACE 2 and associated inflammatory processes, although most patients recover from the acute disease[10,18].

The profile of covid-19 patients outlined in this study was composed predominantly of elderly patients >65 years old (48.95%). Also, they were predominantly male (55.19%), and the most frequent outcome was death (52.19%). These data are similar to those described by Almeida Junior et al.[19], in which the average age of the patients was 66.8 years old, 65.6% were male, and 44% died. In the studies carried out by Nascimento et al.[12] and by Buffon et al. [20], the profiles were, respectively, averages of 66 and 64 years old, 63.9% and 55.5% of male patients, and finally, 24% and 55% of deaths.

Among the comorbidities identified, hypertension was present in 63.9% of the patients, followed by diabetes at 30.8%, obesity at 19.3%, cardiovascular diseases at 17.2%, and finally, kidney disease at 9.0%, whether associated or not. The prevalence of such comorbidities was also observed by Nascimento et al.[12], who obtained data on hypertension (55.7%) and diabetes mellitus (27.8%) as highlights. The data on hypertension (59%), obesity (41%), and diabetes mellitus (41%) were also highlighted in Buffon et al.'s[20] study.

The evolution of myocardial injury in SARS-CoV-2 patients occurs according to the severity and extent of the disease triggered in the clinical picture of systemic inflammation [5]. The higher Troponin I values obtained in this study relate significantly to hypertension, with a mean of 1310.47 ng/L, p-value=0.041, and to kidney disease, with a mean of 4204.36 ng/L, p-value=0.732.

The higher mean of Troponin I values was significant in patients who were discharged compared to patients who died (p-value <0.0001). However, it is not acknowledged in this study what the subsequent analyses of the Troponin I dosage throughout hospitalization were, as well as any medical complications and coronary events that increase Troponin I values (for example, the influence of risk factors).

The multicenter study by Rutledge et al.[11] indicated troponin dosage as a useful biochemical marker associated with a worse prognosis for covid-19 (initial TnT

concentration >64 ng/L) and related to a 37% increased chance of in-hospital death. In the study carried out by Maino et al.[21], the patients who died had a mean TnI of 46.0 ng/L (12-5184 ng/L, p <0.001), with a high standard deviation of the dosed mean of Troponin I. This result is similar to the present study, in which the variation of Troponin I values within the 99th percentile was linked to death during hospitalization.

For Al Abassi et al.[22], patients with elevated Troponin I levels were older (77±13 years) and more likely to have a history of hypertension, diabetes mellitus, and chronic heart failure. Patients with elevated Troponin I levels within the first 24 hours of admission (52%) were likely to have higher in-hospital mortality due to covid-19. The present study found a significant mortality rate in patients older than 65 years of age (62% of recorded deaths) and obtained a similar history of listed comorbidities.

Chronic diseases, such as hypertension and cardiovascular disease (CVD), share common physiological states with infectious diseases, such as a pro-inflammatory state and attenuation of the innate immune response, which makes individuals more susceptible to health problems and cardiac damage. It is worth mentioning that hospital mortality in hypertensive patients is much higher than in normotensive patients[23,24]. Out of the patients analyzed in this study, 63.93% were hypertensive. However, the outcome of death in hypertensive patients was not significant (p-value = 0.847), and it was possible to attribute the deaths to other metabolic dysfunctions.

The prevalence of non-coronary conditions associated with increased cardiac troponins and without SARS-CoV-2 infection occurs especially in the elderly population[4], in which both coronary and non-coronary cardiac pathologies are found. According to Domingues et al.[25] high Troponin levels were not related to coronary syndromes but rather to a high-risk clinical profile, with wide heterogeneity regarding the main diagnosis and prognosis. The present study corroborates the high-risk clinical profile since 17.21% of the patients who had cardiovascular disease, 63.49% died.

Regarding kidney disease patients, there was a prevalence in Troponin I means (4204.36 ng/L) despite the low incidence in the population assessed (9.5% of participants). Such value is attributed to the various mechanisms that trigger cardiac injury. In the study by Maino et al.[21] only 9.02% of the population presented such comorbidity. In addition, they found cardiovascular risk factors in 55.3% of the patients. The most frequent factor was hypertension (42.3%), followed by dyslipidemia (17.5%) and diabetes (14.8%), which is similar to the results obtained in the present study.

For Khaloo et al.[3], there is evidence of primary non-cardiac etiologies for Troponin elevation, such as renal failure and chronic diseases. However, currently, there are no guidelines for interpreting altered results in patients with kidney disease and covid-19[26]. Lozano et al.[27] suggested that acute kidney injury is a risk factor for death in Intensive Care Unit patients with such viral disease.

The exact mechanism of Troponin elevation is uncertain. Such elevation may occur due to increased release of the biomarker by the heart and decreased renal elimination triggered by renal reabsorption of such proteins. However, troponin concentration would be constant if its accumulation was due to transient renal injury[28]. According to Szczykowska et al. [29], the more advanced the renal failure, the stronger the relationship is between increased Troponin level and mortality since renal failure without Troponin change is rare in hospitalizations for covid-19. This was proven in the present study, in which only 9.02% of the patients had kidney disease associated with the highest mortality rate.

Patients with decreased estimated glomerular filtration rate (eGFR <60 ml/min/1.73m^2) and no history of acute coronary syndrome or congestive heart failure often have altered troponin levels in covid-19 infection[29]. These data are aligned with the results obtained in the present study (eGFR=49.5±35.1 mL/min/1.73m^2). The mean eGFR in the cases of renal patients' deaths was 39.56.1 mL/min/1.73m^2. However, Lozano et al.[27] obtained the value of eGFR=84.1±25.7 mL/min/1.73m^2 in the classification of acute

kidney injury in a study on risk factors in covid -19.

The correlation between troponin and eGFR presented in this study was significantly negative, which evidences the elevation of troponin levels due to cardiac injury regardless of the decreased renal clearance and subsequent accumulation of serum Troponin. It was emphasized in the study by Lozano et al.[27] that impaired renal function is not the main factor behind the elevation in Troponin levels, and extensive diagnostic investigation is necessary in all patients with elevated troponin levels, regardless of their eGFR.

CONCLUSION

By means of Troponin I dosages as a laboratory criterion, cardiac injury was observed in 46.86% of the patients hospitalized by covid-19. The outcomes of death can mainly be attributed to elderly people with elevated serum Troponin I concentration on hospital admission. The most evident comorbidity was hypertension, while the highest mean mortality rate was identified in people with kidney diseases and decreased eGFR.

Finally, the study's limitations were the extreme values of Troponin I with no significant relation to covid-19, which may influence the means and standard deviations obtained. For future perspectives, further studies can explore other data to complement the present results, as well as elucidate the mechanisms involved in the Troponin I elevation and outcome of the hospitalized patient.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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