Global Journal of Medical Research: F
Diseases
Volume 24 Issue 1 Version 1.0 Year 2024
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Exploring Biomarkers for Early Prognosis of COVID-19-Induced Acute Kidney Injury: A Comprehensive Systematic Review

By Bruna Morais de Souza Neves, Venine Prado Saêta, Thaís Reis Oliveira, Lilian Carla Carneiro & Nadya da Silva Castro Ragagnin

Federal University of Goiás

Abstract- Acute kidney injury (AKI) is one of the main secondary manifestations developed in patients with COVID-19. Based on this aspect, the present study aimed to identify the main biomarkers used to predict acute kidney injury and prognosis in COVID-19 and gather information about the biomarkers studied. Articles published in the Virtual Health Library, between January 2020 and February 2022, in English, Portuguese and Spanish were evaluated, with the guiding question "What is the scientific evidence on new biomarkers for diagnosis and determination of the prognosis of induced acute kidney injury?" in COVID-19?". Initially, more than 75 thousand articles were identified, however, with the attribution of inclusion and exclusion criteria, 8 articles were selected and analyzed during the present study. The findings of the present review emphasize that early diagnosis has a strong influence on the prognosis of AKI and that new biomarkers are useful for detecting and predicting the prognosis of the injury early. The potential of these assays with new biomarkers proved to be significant and could allow their use in future research.

Keywords: *acute kidney injury, biomarkers, COVID-19, diagnosis, glomerular filtration, performance, prognosis, secondary manifestations, serum creatinine.*

GJMR-F Classification: *NLM Code: WJ 300-378*

Strictly as per the compliance and regulations of:

Exploring Biomarkers for Early Prognosis of COVID-19-Induced Acute Kidney Injury: A Comprehensive Systematic Review

Bruna Morais de Souza Neves [α], Venine Prado Saêta [σ], Thaís Reis Oliveira [ρ], Lilian Carla Carneiro [ω] & Nadya da Silva Castro Ragagnin [¥]

Abstract- **Acute kidney injury (AKI) is one of the main secondary manifestations developed in patients with COVID-19. Based on this aspect, the present study aimed to identify the main biomarkers used to predict acute kidney injury and prognosis in COVID-19 and gather information about the biomarkers studied. Articles published in the Virtual Health Library, between January 2020 and February 2022, in English, Portuguese and Spanish were evaluated, with the guiding question "What is the scientific evidence on new biomarkers for diagnosis and determination of the prognosis of induced acute kidney injury?" in COVID-19?". Initially, more than 75 thousand articles were identified, however, with the attribution of inclusion and exclusion criteria, 8 articles were selected and analyzed during the present study. The findings of the present review emphasize that early diagnosis has a strong influence on the prognosis of AKI and that new biomarkers are useful for detecting and predicting the prognosis of the injury early. The potential of these assays with new biomarkers proved to be significant and could allow their use in future research.**

Keywords: acute kidney injury, biomarkers, COVID-19, diagnosis, glomerular filtration, performance, prognosis, secondary manifestations, serum creatinine.

I. Introduction

During the COVID-19 pandemic, part of the individuals infected with SARS-CoV-2 manifested a mild to moderate respiratory illness, however, many elderly people and people with other comorbidities evolved to severe conditions[1]. Patients in the intensive care unit (ICU) developed secondary complications, such as liver damage, venous thromboembolism, acute kidney injury (AKI), and others[2]. AKI in this case is correlated with poor prognosis and a higher risk of patient mortality[3].

Currently, the definition and staging of acute kidney injury are based on the KIDGO (Kidney Disease Improving Global Outcomes) criteria, which unifies the RIFLE (Risk, Injury, Failure, Loss and End-Stage) and AKIN (Acute Kidney Injury Network) criteria[4]. Thus, KDIGO uses changes in serum creatinine and urinary output, requiring at least two serum creatinine values obtained in 48 hours[5].

Serum creatinine levels increase as a 50% drop in renal function occurs, that is, it is not directly correlated with the decrease in glomerular filtration rate (GFR), which makes early diagnosis impossible[6]. Given this, in recent years, studies with new biomarkers for AKI have gained emphasis in different clinical settings. Among the new biomarkers tested are: Cystatin C, Lipocalin Associated with Human Neutrophil Gelatinase (NGAL), N-acetyl -B-D-glucosaminidase (NAG), Kidney Injury Molecule-1 (KIM-1), Interleukin-18 (IL -18), Netrin-1 and others[7,8].

Given the difficulty of diagnosing AKI using serum creatinine and the inefficient prognosis in COVID-19, the use of biomarkers such as Cystatin C and interleukin-18 is suggested[9]. Cystatin C is a cysteine proteinase inhibitor protein, which is related to several pathological processes. It is freely filtered in the glomeruli, as it has a low molecular weight, but is almost completely reabsorbed in the proximal tubules[10]. Interleukin-18 is a pro-inflammatory cytokine that induces the release of inflammatory cytokines and TNF, thus acting as a mediator in the immune system[6].

The present work is a systematic review of the comprehensive literature, with the main objective of exploring biomarkers for the early diagnosis of AKI induced by COVID-19. Predicting and/or determining the patient's prognosis, as this is of clinical importance and is extremely necessary to apply as a laboratory practice.

II. Methods

a) Instrument for selection of studies and inclusion criteria

The instrument for selecting the studies was the Relevance Test (TR), based on Pereira's model (2006)[11]. This consists of forms containing four selection steps, to include or exclude the articles found with the search strategy.

Initially, TR1 was applied to the references to select studies that meet the following inclusion criteria:

- Publications made from January 2020 to February 2022;
- Published in Portuguese, English and Spanish.

Author α ¥: University Federal of Jataí, Goiás, Brazil.
Author σ ρ: Graduate Program in Health Sciences, Federal University of Goiás, Goiás, Brazil. e-mail: veninesaeta@hotmail.com
Author ω: Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiás, Brazil.

TR2 was applied in the title and abstract of the studies, with the help of the search platform. At this stage, the defined inclusion criteria were: primary and complete article; study with humans; work with biomarkers; study with COVID-19 or SARS-CoV-2.

TR3 was applied only in the abstract of articles containing the following inclusion criteria: studies that address AKI in people diagnosed with COVID-19; and studies using renal biomarkers.

TR4 is the final step of the procedure, which was applied to the entire article and intended to answer the following questions defined as inclusion criteria: Was the kidney disease due to COVID-19? Were there specific biomarkers for AKI? Was there a correlation between changes in biomarkers and prognosis for AKI-COVID?

As exclusion criteria, those who did not meet the criteria described above were considered.

b) Definition of descriptors and search in the literature

A literature search was performed by crossing the following descriptors in Health Sciences/Medical Subject Headings (DeCS/MeSH) available on the VHL network: Acute Kidney Injury and COVID-19 "*OR*" SARS-CoV- two. The articles were searched using the advanced method, using the term "title/abstract/subject" with the combination of descriptors and the Boolean operators "*AND*" and "*OR*".

c) Data extraction and analysis

Taking into account the methodological rigor of a systematic literature review (SLR), a form was prepared to extract the following information from the included studies: bibliographic reference, type of study, research objectives, methodology, and results obtained[12]. To synthesize as much information as possible about the biomarkers for the prognosis of AKI, the following data were collected: characteristics and clinical conditions of the patients, criteria for diagnosing AKI, biomarkers used, the value of the biomarker and serum creatinine on admission and whether there was any change in the glomerular filtration rate (GFR), biomarker performance for AKI prognosis and clinical outcomes.

III. Results

Bearing in mind that new articles are inserted in the databases every day, April 24, 2022, was chosen to carry out the bibliographic research of this RSL. A total of 75,631 articles were obtained, of which TR1 was applied. After applying the first test, a total of 13,531 articles were included, in which the TR2 was applied in the titles and abstracts with the help of the search platform, 12,492 studies were excluded and 1,039 were included. In the next step, TR3 was applied to the abstracts of previously selected articles, which resulted in several 30 selected. All 30 articles were accessed in full, so TR4 was applied to these by reading the full article, which resulted in the exclusion of 22 articles and the inclusion of 08 articles for this review. Finally, the 08 articles were submitted for analysis and data extraction, as shown in Figure 1.

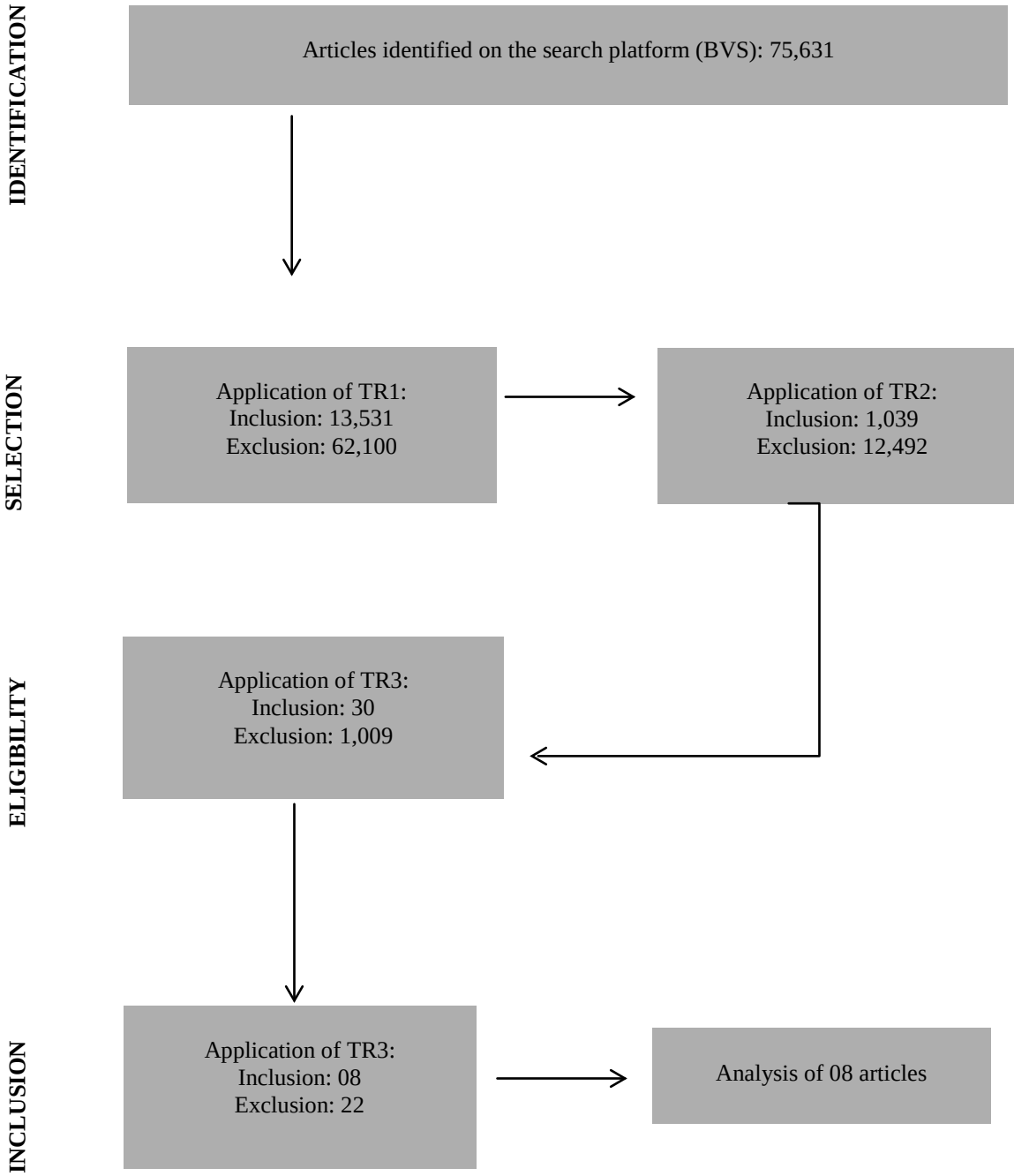

Figure 1: Methodological approach used in the Systematic Review of the Literature on biomarkers for the prognosis of acute kidney injury induced by COVID-19 (BVS, 2022).

After analyzing the eight studies selected for this SLR, a summary of the general characteristics was prepared and made available in synoptic tables. In Frame 1, information and characteristics of the articles analyzed during the study are presented.

Frame 1: Information and characteristics of the articles selected during the study

Reference	Study design	Selection of participants
Temiz *et al*. (2022)	A prospective pilot study	Participants were selected from the urology and ICU departments suspected, suspected of COVID-19 and with specific findings on tomography
Shakked *et al.* (2022)	Prospective observational investigation	Adults (≥18 years) and patients who test positive for Covid-19
Husain-Syed *et al*. (2021)	Prospective, observational, single-centre study	Patients were included if they consented to the linkage with administrative data for longterm follow-up
Gradin *et al*. (2021)	Study is a sub-study of a larger prospective observational	Adult patients with COVID-19 admitted to the ICU and with informed consent, in addition to urinary samples included in the study
Vogel *et al.* (2021)	Cohort of COVID-19 patients in this prospective observational clinical trial	Patients presenting with acute symptoms of respiratory infection. The secondary outcome was a composite of acute kidney injury, ICU admission, and death
Indirli *et al.* (2022)	A single-centre, observational, retrospective, case–control study	Data were retrospectively extracted from the COVID-19 Network registry
Fukao *et al*. (2021)	Retrospective study	Used data from all patients with COVID-19 seen
Wang *et al*. (2021)	Prospective observational investigation	Patients admitted to for COVID- 19, were eligible for this study

Biomarker predictors of poor prognosis such as ICU stay, renal replacement therapy (RRT), or death were observed for patients with AKI in COVID-19, as shown in Frame 2.

Frame 2: Prognostic predictor biomarkers for AKI in COVID-19

Reference	Biomarker	Prognosis
Temiz *et al*. (2022)	KIM-1/creatinine and NGAL/creatinine	Death
Shakked *et al.* (2022)	Serum creatinine Serum cystatin C and NGAL	AKI AKI aggravation RRT needs Admission in ICU
Husain-Syed *et al*. (2021)	Urinary DKK33	AKI Chronification
Gradin *et al*. (2021)	Serum creatinine Urinary KIM-1 Urinary NGAL	Correlation with urinary cytokines AKI aggravation
Vogel *et al.* (2021)	Serum creatinine urinary KIM-1 urinary NAG	AKI, ICU e Death
Indirli *et al.* (2022)	MR – Serum ProADM serum copeptin	Sepsis and AKI; Death, ICU or Hospital complications.

DKK33 Dickkopf-related protein 3*, KIM-1* Kidney Injury Molecule 1*, AKI* Acute Kidney Injury*, NAG* N-acetyl-β-D-glucosaminidase*, NGAL* Neutrophil gelatinase-associated lipocalin*, MR – ProADM* Mid-regional pro-adrenomedullin*, TRS* Therapy Renal replacement*, ICU* Intensive care unit.

Two studies evaluated biomarkers that were useful for early diagnosis, these markers are shown in Frame 3.

Frame 3: Biomarkers for early diagnosis

Reference	Biomarker
FUKAO *et al*. (2021)	L-FABP and urinary β2MG
WANG *et al*. (2021)	Serum procalcitonin (PCT)

β2MG β2-microglobulin, L-FABP Liver-type fatty acid binding protein.

When analyzing the characteristics of the clinical conditions of the populations of the eight studies, it was observed that among the eight studies, the size of the population with COVID-19 ranged from 18 to 389 patients, with three studies presenting, in addition to the COVID-19 cohort, a control group, such as can be observed in Table 1.

Table 1: Characteristics and clinical conditions of patients with COVID and AKI

Reference	Sample No.	AKI (%)	Age (average or median + IQ)	Comorbidities
Temiz *et al.* (2022)	75 COVID-19 11 Control	16	55,77 ± 17,47	Hypertension
Shakked *et al.* (2022)	52	42,3	66	Heart failure, hypertension, chronic kidney disease, cerebrovascular disease
Husain-Syed *et al.* (2021)	55	10,45	54	Hypertension, diabetes, chronic kidney disease, coronary artery disease
Gradin *et al.* (2021)	29 COVID-19 9 Control	66	57 ± 3	Hypertension, chronic lung disease, and diabetes mellitus
Vogel *et al* (2021)	54 COVID-19 26 Control	14,8	56,8	Hypertension, chronic lung disease, and diabetes mellitus
Indirli *et al*. (2022)	116	3	66	Hypertension, diabetes, obesity, and coronary artery disease
Fukao *et al.* (2021)	18	11	64,0 (44,0–74,5)	Hypertension, diabetes mellitus, and coronary heart disease
Wang *et al.* (2021)	389	7,8	66 (15)	Hypertension diabetes mellitus, liver disease

In Frames 4 and 5, the general characteristics of six out of eight studies are presented in detail. It was observed that among the eight selected studies, four are prospective and two are retrospective. These studies were carried out in Turkey (1), the United States (1), Germany (2), Sweden (1), Italy (1), Japan (1), and China (1), published among the years 2021 and 2022.

Frame 4: General characteristics of studies with biomarkers for prognosis

Reference	Type of study	Objectives	Methodology	Conclusions
Temiz *et al.* (2022).	Prospective pilot	Investigate whether there is kidney damage during COVID-19; Identify the predictive value of renal biomarkers and estimate survival.	KIM-1/creatinine and NGAL/ creatinine ratios were compared among 36 patients with COVID-19 and 11 controls. Mortality rates were determined using the Kaplan-Meier method.	Urine KIM-1/creatinine ratio associated AKI with COVID-19-specific death. In clinical practice, serum Cystatin C (sCysC) and urine KIM-1/creatinine are associated with survival.
Shakked *et al*. (2022).	Prospective, observational	To evaluate the usefulness of serum CysC (sCysC) and serum NGAL (sNGAL).	Demographic data of 52 patients were retrieved from medical records. sCysC, serum creatinine, and serum and urine NGAL were analyzed.	sCysC was an excellent early predictor of AKI and the need for RRT in patients with COVID-19, but it did not outperform serum creatinine. While sNGAL showed good performance for the diagnosis of AKI.
Husain-Syed *et al*. (2021).	Prospective, observational	Evaluate the role of renal biomarkers to monitor the progression of COVID-19.	Spot urine samples were collected from 55 patients daily and for analysis of uDKK3 and IL-6 it was collected three times a week from hospital admission until the day of discharge.	Biphasic patterns of urinary uDKK3 and IL-6 in patients with a greater decrease in eGFR are suggestive of a chronification of AKI and commonly used urinary markers may be less suitable.

CysC Cystatin C, eGFR Estimated Glomerular Filtration Rate, IL-6 Interleukin 6, KIM-1 Kidney Injury Molecule 1, AKI Acute kidney injury. NGAL Neutrophil gelatinase-associated lipocalin, RRT Renal replacement therapy, uDKK3 Urinary Dickkopf-3.

Frame 5: General characteristics of studies for early diagnosis of AKI

Reference	Type of study	Objectives	Methodology	Conclusions
Fukao *et al*. (2021).	Prospective observational clinical trial	Investigate relationships of tubular injury, COVID-19 severity, and markers of inflammation To address cytokine-mediated mechanisms in the development of AKI.	Analysis of markers and respiratory status was performed in 18 patients with COVID-19. Correlation analysis among levels of tubular and laboratory markers.	Urinary markers L-FABP and uβ2MG were significantly associated with IL-6 levels even in patients without overt AKI. It is suggested that L-FABP and urinary uβ2MG are useful as early diagnostic biomarkers.
Wang *et al.* (2021).	Exploratory	To assess the value of PCT in predicting AKI during COVID-19. Build a risk classification score.	The biomarker concentrations of 28 patients with COVID-19 were analyzed. A multivariate risk score was created.	Single PCT value is a valuable predictive marker of AKI in patients with COVID-19. The risk score can help assess the possibility of developing AKI.

β2MG β2-microglobulin, IL-6 Interleucina 6, L-FABP Liver-type fatty acid binding protein, AKI Acute kidney injury, PCT Procalcitonin.

After analyzing the studies, it is observed that the classification used for the detection of AKI was KDIGO (2012), having been used in seven of the eight studies found, and only one study did not present this information. Biomarkers were analyzed in blood and urine samples, with analysis of serum biomarkers being the most prevalent among the eight studies. The dosage of these markers was carried out from the moment of consultation in the emergency department or hospital admission. In summary, this information is available in Frames 6 and 7.

Frame 6: Biomarkers for AKI prognosis in patients with COVID-19.

Reference	Biomarker	Serum or urinary	Biomarker value on admission (median ± IQR)	Biomarker performance for early diagnosis and prognosis
Temiz *et al*. (2022)	Creatinine	Serum	0,75 +/- 0,39 (mg/dL)	Elevated KIM-1/creatinine: death from COVID-19.
	Cystatin C	Serum	0,96+/- 0,59 (mg/L)	Higher elevation of urinary KIM-1/creatinine and NGAL/creatinine levels in the ICU. Increased levels: death from COVID-19.
	KIM-1	Urinary	12,95 +/- 5,82 (ng/mL)	Increased uKIM-1/creatinine: death from COVID-19.
	NGAL	Urinary	61,26 +/- 75,35 (ng/mL)	Altered uNGAL/creatinine levels: death from COVID-19.
	KIM-1/ Creatinine	Urinary		Increased levels: death from COVID-19.
			Decrease in GFR	
Shakked *et al.* (2022)	Creatinine	Serum	0,76 (0,71–0,92) (mg/dL)	It was increasingly correlated with the increase in the severity of AKI. AUC: 0.86 to predict AKI and AUC: 0.94 to need RRT.
	Cystatin C	Serum	0,82 (0,74–0,99) (mg/L)	It correlated increasingly with AKI severity. Excellent for predicting AKI (AUC: 0.87) and RRT requirement (AUC: 0.94). Moderate performance in predicting the need for ICU admission.
	NGAL	Serum	57,6 (49,1-95) (ng/mL)	Moderate performance for predicting ARL (AUC: 0.81) and TRS (AUC: 0.87). Significantly elevated levels among patients with severe AKI requiring RRT. Moderate performance in predicting the need for ICU admission.

			Decrease in GFR	
Husain-Syed *et al.* (2021)	Creatinine	Serum	Média + IQR 1,23 (1,04–1,45) mg/Dl	There was no correlation.
	α1MGCR/ Creatinine	Urinary	82,7 (50,2–136,2) mg/g	There was no correlation.
	uDKK33/ Creatinine	Urinary	3781 (1402–10192) pg/g	Biphasic uDKK33 patterns in patients with greater eGFR decline were suggestive of AKI-CKD transition.
	Cystatin C	Serum	1,62 (1,35–1,94) mg/L TFGe ≥5 mL/min/1,73 m	There was no correlation.
Gradin *et al.* (2021)	Creatinine	Serum	68 (62-81) mmol/L	Maximum creatinine correlated significantly with 19 cytokines.
	KIM-1 NGAL	Urinary Urinary	5,3 (2,7 - 10,6) ng/g UCr 33 (13 - 130) U/g UCr	Correlation with many urinary cytokines of incidence and worsening of AKI.
	Cytokines	Urinary		31 cytokines were associated with the maximum stage of AKI, ie, the need for RRT.
			Decrease in GFR	
Vogel *et al.* (2021)	Creatinine	Serum	0,95 (0,77–1,26) mg/Dl	Significant increase in patients who achieved the composite outcome of AKI, ICU, and death.
	KIM-1	Urinary	1316(485–2316) ng/g UCr	Elevated levels in patients who achieved the composite endpoint of acute kidney injury, ICU, and death. For predicting ICU admission, AUC was obtained: 0.76.
	NAG	Urinary	4,75 (1,54–10,7) U/g UCr	Elevated in COVID-19 patients who have suffered from AKI.
			Decrease in GFR	
Indirli *et al.* (2022)	Creatinine	Serum	0,9 (0,7–1,1) mg/Dl	Significant increase in patients achieving the composite endpoint.
	MR-proADM	Serum	0,9 (0,6–1,3) nmol/L	The value on admission was useful for predicting sepsis and AKI during hospitalization.
	Copeptin	Serum	13,2 (6,3–30,8) pmol/L	The value on admission was useful for predicting sepsis and AKI during hospitalization. It was useful for predicting the composite outcome of death, ICU, or hospital complications. Copeptin was associated with length of stay and a more complicated clinical picture.
			Decrease in GFR	

AUC Area under the curve, *α1MGCR* α1-microglobulin-creatinine ratios, *CKD* Chronic kidney disease, *eGFR* Estimated glomerular filtration rate, *KIM-1* Kidney Injury Molecule 1, *MR – ProADM* Mid-regional pro-adrenomedullin, *NAG* N-acetil-β-D-glicosaminidase, *NGAL* Neutrophil gelatinase-associated lipocalin, *AKI* Acute kidney injury, *GFR* Glomerular filtration rate, *RRT* Renal replacement therapy, *uα1MG* Urinary α1 microglobulin, u*DKK3* Urinary Dickkopf-3, *ICU* Intensive care unit.

Frame 7: Biomarkers for early diagnosis of AKI in patients with COVID-19

Reference	Biomarker	Serum or urinary	Biomarker value on admission (median ± IQR)	Biomarker performance for early diagnosis and/or prognosis
Fukao *et al.* (2021)	NAG	Urinary	32,5 U/L	There was no correlation.
	β2MG	Urinary	10.516 μg/L	Elevations in L-FABP and uβ2MG

	α1MG	Urinary	65,8 mg/L	reflected early tubular injury.
	L-FABP	Urinary	47,9 μg/gCr	
	Decrease in GFR			
Wang *et al.* (2021)	Creatinine	Serum	160 (65–293) umol/L	PCT correlated with AKI in patients with COVID-19.
	Procalcitonin	Serum	0,440 (0,133–2,433) ng/ml	
	Urea nitrogen	Serum	15,40 (6,50–30,65) mmol/L	
	Uric acid	Serum	408 (235-670) (umol/L)	
	Decrease in GFR			

α1MG α1 microglobulin, *β2MG* β2-microglobulin, *L-FABP* Liver-type fatty acid binding protein *AKI* Acute kidney injury, *NAG* N-acetil-β-D-glicosaminidase, *PCT* Procalcitonin, *GFR* Glomerular filtration rate.

Regarding the results for prognosis, it was seen that the biomarkers used were predictors of poor prognosis. KIM-1/creatinine and NGAL/creatinine ratios were predictors of death from COVID-19[13]. Serum creatinine and cystatin C were indicators of AKI, worsening of the lesion, and need for RRT. The NAG marker was significant for predicting AKI in patients with severe AKI who required RRT[14]. Elevation in the urinary biomarker uDKK33 at six months from hospital admission was suggestive of AKI chronicity by COVID-19[15]. Serum creatinine and urinary biomarkers KIM-1 and NGAL correlated with urinary cytokines of incidence and worsening of AKI[16]. Serum creatinine and KIM-1 were significantly elevated in patients who achieved the composite endpoint (acute kidney injury, ICU, and death) and the NAG marker was significantly elevated in patients who suffered from AKI[17].

In Frame 7, the results of two studies with biomarkers for the early diagnosis of AKI in COVID-19 are available.

IV. Discussion

The electronic survey involved studies carried out during the COVID-19 pandemic, published between 2021 and 2022. Given the pandemic context, one can observe agility in carrying out the surveys. In addition, according to the analyzed studies, it is observed that the search for new AKI laboratory biomarkers for the identification and progression of AKI continues to advance.

Despite the size of the sample (18 to 389 participants), no influence was verified on the characteristics and clinical conditions of the patients. It was observed that among the eight studies, the patients who developed AKI were over 50 years old, and were hypertensive or diabetic. In addition, the KDIGO diagnostic criteria, GFR calculation using the CKD-EPI formula, and biomarker analysis (ELISA) were also similar among studies. In addition to this, nephelometric tests were also used, mainly to analyze Cystatin C, which helps in the comparison between them. Although unusual, Cystatin C is considered an early marker of AKI and its dosage has been performed with nephelometric tests, as they are considered quite stable[18].

Among the biomarkers, urinary KIM-1 stood out as the most promising for the diagnosis and prognosis of AKI. Significant elevations were found in the KIM-1/urinary creatinine ratio in patients with AKI and specific deaths from COVID-19[13]. Consistently, a significant increase in KIM-1 levels between 24h and 48h after admission to the ICU in patients with septic AKI due to other diseases who did not survive was also verified[19]. In a study by [16], a correlation of urinary KIM-1 with several urinary cytokines related to the incidence and worsening of AKI in COVID-19 was observed. The results of [17] showed elevations in urinary KIM-1 levels in COVID-19-positive patients with a composite outcome of AKI, ICU admission, and death. Similarly, in a study carried out with patients hospitalized with AKI in other diseases, the increase in urinary KIM-1 and NAG levels at the time of consultation with a nephrologist were predictors of the composite outcome of RRT or in-hospital death[20].

The second prominent biomarker was NGAL, both for serum concentrations and urinary levels. Serum NGAL was useful for predicting AKI, need for RRT, ICU stay, and expressly highs in severe AKI requiring RRT[14]. NGAL/creatinine was useful as a good predictor of mortality in patients with COVID-19 and AKI[13]. Similar results were found in a study with critically ill patients due to other diseases, where 40% more cases of AKI were detected with the evaluation of NGAL and creatinine than when using creatinine alone, and in these patients, the risk of ICU admission, need for TRS and death was higher[21,22].

Another biomarker with prognostic results for AKI was sCysC, whose elevation exceeded the urinary KIM-1/creatinine and NGAL/creatinine ratio in ICU patients, but was not considered a predictor of specific mortality from COVID-19[13]. Serum and urine creatinine were used in all eight studies, as it is the standard AKI diagnostic marker. On admission, serum creatinine was similar to sCysC for predicting AKI and the need for

RRT[14]. However, the elevation of sCysC compared to serum creatinine may have been influenced by high doses of corticosteroids[15].

In the analysis of urinary dickkopf-3 (uDKK3), a new biomarker of CKD progression. uDKK3 levels remained high 6 months after hospital admission for COVID-19 in patients with AKI and a greater decline in glomerular filtration. The existence of a secondary AKI over an unresolved AKI has been suggested, which may contribute to the transition from AKI to CKD at 6 months post-discharge15. These findings are similar to what is in the literature, since in a study with post-cardiac surgery patients, urinary DKK3 was associated with a risk of severe loss of glomerular filtration after the transition from AKI to CKD during the patients' follow-up period[23].

As for biomarkers for early diagnosis of AKI, the highlights were β2MG and L-FABP, which were elevated in urine samples as a reflection of the onset of AKI[24]. L-FABP is a protein present in the liver that plays an important role in regulating the metabolism of fatty acids. In addition, it has a high affinity for lipid peroxidation products, which promotes its elimination in the urine[25].

[26] Evaluated common biomarkers, but included serum PCT dosage in their study, which in turn was useful for early detection of AKI in patients with COVID-19[27].

Although the cost of testing may still be a limiting factor, the results have shown promise for assessing the incidence of AKI with new biomarkers[16,28,14,17], predict AKI severity, help identify patients who need RRT[16,14] or ICU[28,14,17], predict death[28,17,13] and perform early detection of AKI in COVID-19[24,26], thus minimizing the cost of the test.

With the use of new biomarkers detected before serum creatinine, it was possible to detail the AKI caused by COVID-19 for the first time in the literature[13]. The evaluation of biomarkers such as KIM-1 and Cystatin C at admission can provide diagnostic data and help to outline the prognosis of AKI, which can influence medical decisions and thus increase the chances of better outcomes[17,14]. In addition, it is considered important to evaluate the renal system in COVID-19 with AKI biomarkers, as well as to consider their continuous evaluation during hospitalization[13].

The application of new sensitive biomarkers for AKI proved to be important for the diagnosis and prognosis of the lesion in the COVID-19 scenario.

Different biomarkers were able to predict AKI severity, need for RRT, hospitalization, and death. The poor prognosis of AKI in COVID-19 observed in the analyzed studies highlights the importance of identifying new biomarkers and applying them in laboratory practice and different clinical scenarios.

Although the use of some of these biomarkers is limited due to the high cost of the necessary reagents, the potential of these assays with new biomarkers has proved to be significant and may enable their use in future assays and research. In addition, to improve the clinical evaluation, aiming to favor clinical outcomes, it is suggested to measure these biomarkers in the first contact with the patient, that is, since the positive test result for SARS-CoV-2.

As observed in the RSL, the prominent marker to predict different outcomes of patients with AKI was KIM-1. Thus, in the future, the use of this biomarker, combined with serum creatinine and other markers, may make the diagnosis of AKI more assertive and identify the risks of worsening AKI early.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research was funded by the Fundação de Amparo à Pesquisa do Estado de Goiás (FAPEG).

References Références Referencias

1. World Health Organization (WHO). WHO-convened global study of origins of SARS-CoV-2: China Part. Genebra, 2021. Available in: https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part.
2. Nicholas JB, Tom EF, Robert F. Doença do coronavírus 2019 (COVID-19). BMJ Best Practice, 2021. Available in: https://bestpractice.bmj.com/topics/pt-br/3000201.
3. Sociedade Brasileira de Nefrologia (SBN) e Associação de Medicina Intensiva Brasileira. Nota técnica e orientações sobre a injúria renal aguda (IRA) em pacientes com COVID-19. São Paulo: 2020. 11 p. Available in: https://www.sbn.org.br/fileadmin/user_upload/sbn/2020/04/15/Nota_tecnica_e_orientacoes_sobre_a_injuria_renal_aguda__IRA__em_pacientes_com_COVID-19.pdf.
4. Levi TM, Souza SP de, Magalhães JG de, Carvalho MS de, Cunha ALB, Dantas JGAO et al. Comparação dos critérios RIFLE, AKIN e KDIGO para predizer mortalidade em pacientes críticos. Revista Brasileira de Terapia Intensiva. 2013; 25(4): 290-6. http://dx.doi.org/10.5935/0103-507x.20130050.
5. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. Clinical Kidney Journal. 2013;6(1):8-14. https://doi.org/10.1093/ckj/sfs160.
6. Macedo E. Biomarcadores na injuria renal aguda. In: Abensur, Hugo (ed.). Biomarcadores na nefrologia. São Paulo: Roche. 2011:1-114. Available in: https://arquivos.sbn.org.br/pdf/biomarcadores.pdf.
7. Peres LAB, Júnior ADC, Schäfer AJ, Silva AL de, Gaspar AD, Scarpari DF et al. Biomarcadores da

injúria renal aguda. Jornal Brasileiro de Nefrologia. 2013; 35(3): 229-36. https://doi.org/10.5935/0101-2800.20130036.
8. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Clinical Chemistry and Laboratory Medicine (CCLM). 2017; 55(8): 1074-89. https://doi.org/10.1515/cclm-2016-0973.
9. Koza, Y. Acute kidney injury: current concepts and new insights. Journal of Injury And Violence Research. Journal of Injury and Violence Research. 2016; 8(1): 58-62. http://dx.doi.org/10.5249/jivr.v8i1.610.
10. Okay TS. Cistatina C: Um novo marcador de função renal em crianças. Revista da Associação Médica Brasileira. 2002; 48(2): 93-117. https://doi.org/10.1590/S0104-42302002000200025.
11. Pereira AL. Revisão sistemática da literatura sobre produtos usados no tratamento de feridas. Dissertation (Master's) - Faculty of Nursing, Federal University of Goiás, Goiânia, 2006, 129 p.
12. Pedroso, LA. Utilização de biomarcadores no diagnóstico precoce de lesão renal aguda em pacientes criticamente enfermos: revisão sistemática da literatura. Dissertação (Mestrado) - Curso de Farmácia, Pós-Graduação, Universidade Federal de Minas Gerais, Belo Horizonte, 2017. Cap. 5. Available in: https://repositorio.ufmg.br/bitstream/1843/BUOS-B32JG9/1/disserta__o_luana_pronta_ppgmaf_.pdf.
13. Temiz MZ, Hacibey I, Yazar RO, Sevdi MS, Kucuk SH, Alkurt G et al. Altered kidney function induced by SARS-CoV-2 infection and acute kidney damage markers predict survival outcomes of COVID-19 patients: a prospective pilot study. Renal Failure. 2022; 44(1): 233-40. https://doi.org/10.1080/0886022X.2022.2032743.
14. Shakked NP, Oliveira MHS de, Cheruiyot I, Benoit JL, Plebani M, Lippi G. Early prediction of COVID-19-associated acute kidney injury: Are serum NGAL and serum Cystatin C levels better than serum creatinine? Clinical Biochemistry. 2022; 102:1-8. Available in: https://doi.org/10.1016/j.clinbiochem.2022.01.006.
15. Husain-Syed F, Villa G, Wilhelm J, Samoni S, Matt U, Vadász I et al. Renal markers for monitoring acute kidney injury transition to chronic kidney disease after COVID-19. Nephrology Dialysis Transplantation. 2021; 36(11): 2143-47. https://doi.org/10.1093/ndt/gfab235.
16. Gradin A, Andersson H, Luther T, Anderberg SB, Rubertsson S, Lipcsey M et al. Urinary cytokines correlate with acute kidney injury in critically ill COVID-19 patients. Cytokine. 2021; 146: 155589. https://doi.org/10.1016/j.cyto.2021.155589.
17. Vogel MJ, Mustroph J, Staudner ST, Leininger SB, Hubauer U, Wallner S et al. Kidney injury molecule-1: a potential biomarker of acute kidney injury and disease severity in patients with COVID-19. Journal of Nephrology. 2021; 34(4): 1007-18. https://doi.org/10.1007/s40620-021-01079-x.
18. Neto OAF. Avaliação da Cistatina C como marcador precoce de lesão renal guda em pós-operatório de cirurgia cardíaca pediátrica com uso de circulação extracorpórea. Dissertação (Mestrado) - Universidade Federal de Mato Grosso do Sul, Campo Grande, 2013. Available in: https://repositorio.ufms.br/bitstream/123456789/1912/1/Oreste.pdf.
19. Tu Y, Wang H, Sun R, Ni Y, Ma L, Xv F et al. Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Renal Failure. 2014; 36(10): 1559–63. https://doi.org/10.3109/0886022X.2014.949764.
20. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H et al. Urinary N-Acetyl-β-(D)-Glucosaminidase Activity and Kidney Injury Molecule-1 Level Are Associated with Adverse Outcomes in Acute Renal Failure. Journal of the American Society of Nephrology. 2007; 18(3): 904-12. https://doi.org/10.1681/ASN.2006030221.
21. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DR, Wagener G et al. The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury. Journal of the American College of Cardiology. 2011; 57(17): 1752-61. https://doi.org/10.1016/j.jacc.2010.11.051.
22. Krishnasamy S, Sinha A, Bagga A. Management of Acute Kidney Injury in Critically Ill Children. Indian Journal of Pediatrics. 2023; 90: 481-91. https://doi.org/ 10.1007/s12098-023-04483-2.
23. Schunk SJ, Speer T, Petrakis I, Fliser D. Dickkopf 3—a novel biomarker of the "kidney injury continuum". Nephrology Dialysis Transplantation. 2020; 36(5): 761-7. https://doi.org/10.1093/ndt/gfaa003.
24. Fukao Y, Nagasawa H, Nihei Y, Hiki M, Naito T, Kihara M et al. COVID-19-induced acute renal tubular injury associated with elevation of serum inflammatory cytokine. Clinical and Experimental Nephrology. 2021; 25(11): 1240–6. https://doi.org/10.1007/s10157-021-02101-z.
25. Silva S da. O papel dos biomarcadores TIMP-2, IGFBP7 e L-FABP no diagnóstico da lesão renal aguda. Trabalho de Conclusão do Curso (Graduação) – Curso de Farmácia, Universidade Federal de Santa Catarina, Florianópolis. 2020. Available in: https://repositorio.ufsc.br/bitstream/handle/123456789/218407/TCC%202%20Suzana%20-%20Vers%c3%a3o%20BU%20%281%29.pdf?sequence=1&isAllowed=y.
26. Wang RR, He M, Kang, Y. A risk score based on procalcitonin for predicting acute kidney injury in COVID-19 patients. Journal of Clinical Laboratory

Analysis. 2021; 35(6): e23805. https://doi.org/10.1002/jcla.23805.
27. Castro MC de, SILVA MR da. Procalcitonina no diagnóstico de doenças infecciosas. Rev Bras Clin Med. 2012; 10(6): 521-8. Available in: http://files.bvs.br/upload/S/1679-1010/2012/v10n6/a3188.pdf.
28. Indirli R, Bandera A,Valenti L, Ceriotti F, Modugno AD, Tettamanti M et al. Prognostic value of copeptin and mid-regional proadrenomedullin in COVID-19-hospitalized patients. European Journal of Clinical Investigation. 2022; 52(5): e13753. https://doi.org/10.1111/eci.13753.