REVIEW ARTICLES

An epidemiologic overview of acute kidney injury in intensive care units

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SUMMARY

INTRODUCTION: *Acute kidney injury (AKI) is a frequent event among critically ill patients hospitalized in intensive care units (ICU) and represents a global public health problem, being imperative an interdisciplinary approach.*

OBJECTIVE: *To investigate, through literature review, the AKI epidemiology in ICUs.*

METHODS: *Online research in Medline, Scientific Electronic Library Online, and Latin American and Caribbean Literature in Health Sciences databases, with analysis of the most relevant 47 studies published between 2010 and 2017.*

RESULTS: *Data of the 67,033 patients from more than 300 ICUs from different regions of the world were analyzed. The overall incidence of AKI ranged from 2.5% to 92.2%, and the mortality from 5% to 80%. The length of ICU stay ranged from five to twenty-one days, and the need for renal replacement therapy from 0.8% to 59.2%. AKI patients had substantially higher mortality rates and longer hospital stays than patients without AKI.*

CONCLUSION: *AKI incidence presented high variability among the studies. One of the reasons for that were the different criteria used to define the cases. Availability of local resources, renal replacement therapy needs, serum creatinine at ICU admission, volume overload, and sepsis, among others, influence mortality rates in AKI patients.*

KEYWORDS: *Acute kidney injury. Intensive care units. Epidemiology. Risk factors.*

INTRODUCTION

Acute kidney injury (AKI) occurs most frequently in critically ill patients admitted to an intensive care unit (ICU) and represents a global public health problem.[1,2] The implications of AKI go beyond the care context and involve considerable expenditure for health care institutions and systems, as well as contributing to a reduction in patients' quality of life. [3,4] In 2014, the International Society of Nephrology launched the "0by25" Project, aiming to reduce avoidable death due to AKI worldwide by promoting universal actions and encouraging scientific dissemination on the subject.[5] Thus, this study aimed to investigate the AKI epidemiology in ICUs.

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METHODS

We searched the MEDLINE, Scientific Electronic Library Online, and Latin American and Caribbean Literature in Health Sciences databases for original articles published in English, Portuguese, and Spanish, with information available about the incidence or mortality of critically ill AKI patients admitted to ICUs. The keywords used in the search were: "acute kidney injury", "intensive care unit", and, "epidemiology" with the application of the Boolean operator "AND." The search occurred between January to February 2018.

RESULTS

Forty-seven studies analyzing data from 67,033 patients from more than 300 ICUs located in different regions of the world were included in this review. The overall incidence of AKI ranged from 2.5%[6] to 92.2%[7] and mortality from 5%[8,9] to 80%, reaching 100% in patients who undergo renal replacement therapy (RRT).[10-12]

Among the papers included in this review, 28 reflect data from developing countries, 17 from developed nations, and 2 are multinational, including countries with different income categories. The mean AKI incidence in developed and developing countries was 33.4% and 37.7%, while the mean mortality rate was 40.6% and 43.2%, respectively.

The need for RRT was between 0.8%[13] and 59.2%[14] and the ICU, and hospital stay length varied from [52,15] to 21 days[16] and from 102 to 36 days,[17] respectively. Overall, AKI patients showed a risk of mortality almost 50% higher than patients without AKI, and their hospital stay was up to ten days longer (see Table 1).

DISCUSSION

The use of different diagnostic criteria is one of the factors that contributed to the discrepancies observed in the studies in AKI incidence rate.[18,19] About the geographical location, we verified that AKI-associated mortality rate was higher in developing countries. As demonstrated by another international multicenter study,[2] the risk of death in cases of AKI in ICU is four-fold higher in emerging countries, mainly due to the limited resources available for the adequate/early management of the event.

The AKI occurrence in ICU increases length of stay, need for more vasopressors drugs and specialized human resources, increasing the cost of services and health care systems. The limitation of all these resources and the observed reality in emerging countries contribute to the increase in patients' morbidity and mortality in regions with lower resources.

Furthermore, the population and the total number of participants included in a study should also be considered. A study reported AKI incidence of 2.5% based on data from approximately 8,000 patients enrolled from the database Multiparameter Intelligent Monitoring in Intensive Care-II.[6] Whereas, in a study analyzing data from a single-center survey with 51 patients in the postoperative period of cardiac surgery had an incidence higher than 90%.[7]

In two recent multinational, multicenter studies[1,2] included in this review, the mean incidence of the event was 40.5%, and the mean ICU mortality was 23%, reaching more than 30% among cases that required RRT. In another multinational study published in 2005, AKI incidence in critically ill patients was close to 6%, the need for RRT was higher than 70%, and the mortality predicted in the ICU was 45.6%.[20]

These data show that the burden of AKI worldwide is alarming and has been increasing over the past ten years, requiring that the biomedical model of care be replaced by an interdisciplinary health care model, in which actions are planned by a multi-professional health team. In addition, physicians of different specialties (intensivists, nephrologists, and others) should work with a specialized nursing team, pharmacists, physiotherapists, and nutritionists, each bringing their specific professional expertise to integrate quality intensive care.[1-4]

The demographic transition that has taken place in developed nations and, more recently in developing countries, has also brought clinical-epidemiological changes in the population profile, expressed by the increase in the life expectancy of individuals. Old age and chronic diseases are among the main AKI risk factors, as they result in systemic and permanent metabolic-physiological alterations that lead to decreased basal organic-functional kidney activity.[21] However, these changes have also incurred an increase in the burden brought about by chronic-degenerative pathological conditions.[22]

Zhou et al.[23] reported a significant risk for incidence or death from AKI in ICU among individuals over 50 years of age. However, other studies have shown that morbidity and mortality are especially high among individuals older than 60, and the risk

TABLE 1. SUMMARY OF INFORMATION ABOUT THE EPIDEMIOLOGY OF AKI PRESENTED IN THE REVISED ARTICLES*.

Ref	Patients		Criteria for AKI	Epidemiological data of AKI								
	n	Setting		Incidence (%)	RRT (%)	Mortality endpoint	Mortality (%)			Length of stay (days)		
							With AKI	Without AKI	Diff.	With AKI	Without AKI	Diff.
[1]	1,802	GP	KDIGO	57.3	23.5	ICU Hospital	24 26.9	4.7 7.2	+19.3 +19.7	ICU: 6 Hospital: 15	4 12	+2 +3
[2]	6,647	GP	AKIN-m	DC: 19.1 EC: 19.9 Both: 19.2	15.5 30.2 23.7	Hospital	DC: 27.6 EC: 17.6 Both: 22 RRT: 32.3	NS	-	UTI: DC: 5 EC: 6 Hospital: DC: 11 EC: 10	NS	-
[6]	8,085	GP	KDIGO	2.5	45	NS	NS	NS	-	NS	NS	-
[7]	51	Post-surgery cardiac	KDIGO	92.2	NS	NS	NS	NS	-	NS	NS	-
[8]	1,087	Post-surgery myocardial injury	KDIGO	5.2	NS	30 days	5.3	NS	-	NS	NS	-
[9]	7,696	Volume overload	KDIGO sCr-a	24.2 25.3	NS	60 days	5.4	NS	-	NS	NS	-
[10]	73	HIV	RIFLE	All	23.3	ICU	75.3	-	-	1	-	-
[11]	269	GP versus Sepsis	RIFLE	GP: 8.9 Sepsis: 32.3	AKI: 1.9 AKI+Sepsis 15	ICU	AKI: 66.7 AKI+ Sepsis: 80	GP: 21.2 Sepsis: 45.2	+45.5 +34.8	AKI: 8 AKI+Sepsis 11	GP: 9 Sepsis: 13	-1 -2
[12]	152	GP	RIFLE	65.8	12.4	ICU	AKI: 52 RRT: 84.2	5.8	+46.2	8.5	7	+1.5
[13]	476	GP	AKIN	52.7	0.8	ICU	58	27.5	+30.5	NS	NS	-
[14]	414	Severe acute pancreatitis	AKIN	69.3	59.2	ICU	44.9	20.5	+24.4	24	22	+2
[15]	389	Cancer	KDIGO	Cr: 49.4 UO: 56.3 Both: 69.4	5.9	ICU 180 days	30 51.5	5 15.1	+25 +36.4	5	2	+3
[16]	122	V+P versus V+C	AKIN	V+P: 32.7 V+C: 28.8	V+P: 18.8 V+C: 38.1	NS	NS	-	-	V+P: 17.8 V+C: 21.4	-	-
[17]	74	RRT	NS	27	All	NS	NS	-	-	ICU: 18 Hospital: 36	-	-
[23]	1,036	GP	RIFLE AKIN KDIGO Cys-C	26.4 34.1 37.8 36.1	NS	28 days	57.9 54.4 51.8 52.1	NS	-	13.5 12.9 13.9 13.2	(±) 5	+8.5 +7.9 +8.9 +8.2
[24]	200	Elderly (>60 years)	KDIGO	27	NS	ICU	48.1	15.7	+32.4	11.4	5.2	+6.2
[25]	137	Sepsis	AKIN	77	23.4	ICU Hospital 28 days	39 45 38	NS	-	NS	NS	-
[26]	573	Volume overload	SOFA	23	50.8	28 days	50	13.4	+36.6	15.3	NS	-
[27]	1,234	RRT	RIFLE/ AKIN	All	All	ICU	69.4	-	-	9.8	-	-
[28]	14,986	Obesity	KDIGO	21.1	NS	Hospital 1 year	10 12	NS	-	NS	NS	-
[29]	832	GP	CrCl/ AKIN	CrCl: 58.3 AKIN: 27	CrCl:9.5 AKINNS	ICU	CrCl: 26.2 AKIN: NS	CrCl: 10.7 AKIN: NS	+15.5 -	CrCl: 13.5 AKIN: NS	CrCl: 10 AKIN: NS	+3.5 -
[30]	190	GP	RIFLE AKIN KDIGO	62.6 63.2 63.2	NS	ICU	42.9 42.5 42.5	17.7 17.7 17.74	+25.2 +24.8 +24.8	NS	NS	-
[31]	335	CIN	RIFLE	15.5	34.6	ICU Hospital	40.4 53.8	21.3 35.7	+19.1 +18.1	ICU: 14	ICU: 15	-1
[32]	41	RRT	RIFLE	All	All	ICU Hospital	48.8 53.7	-	-	9	-	-
[33]	548	GP	RIFLE	17.2	4.3	28 days	49	NS		NS	NS	-
[34]	254	Infections diseases	RIFLE	All	27.6	ICU	62.8	-	-	NS	-	-
[35]	3.107	GP	RIFLE/ AKIN/ KDIGO	46.9 38.4 51	(±) 20	Hospital	27.8 32.2 27.4	7 7.1 5.6	+20.8 +25.1 +21.8	5	3	+2
[36]	2,526	GP	KDIGO	46.4	18.9	28 days	25.7	10.1	+15.1	7	5	+2

CONTINUATION

Ref	Patients		Criteria for AKI	Epidemiological data of AKI								
	n	Setting		Incidence (%)	RRT (%)	Mortality endpoint	Mortality (%)			Length of stay (days)		
							With AKI	Without AKI	Diff.	With AKI	Without AKI	Diff.
[37]	65	GP	RIFLE/ AKIN	All	48	ICU	69	NS	-	NS	NS	-
[38]	901	Trauma	AKIN	6	19	30 days	29.6 RRT: 50	7.9	+21.7	NS	NS	-
[39]	114	CIAI	AKIN	58.8	28.9	ICU 28 days	17.9 23.9	NS	-	NS	NS	-
[40]	360	GP	AKIN	59.7	(±) 2.3	ICU	(±) 60.2	18.6	+41.6	ICU (±): 11.9 Hospital: (±) 22.7	ICU: 7.2 Hospital: 27.2	+4.7 -4.5
[41]	715	GP	RIFLE	16.1	39.1	ICU 28 days	7.8 49.5	NS	-	ICU: 11	NS	-
[42]	40	RRT	NS	All	All	30 days	52.5	-	-	NS	-	-
[43]	44	GP	AKIN	All	43.2	ICU	43.2	NS	-	NS	NS	-
[44]	627	GP	RILE/ AKIN	RIFLE: 69.4 AKIN: 51.8 Both: 74.4	5.4	90 days	40.9 44.6	19.8 23.5	+21.1	14	14	-
[45]	149	CIN	RIFLE	15.4	13	ICU	52	19	+33	13	12	+1
[46]	2,901	GP	AKIN/ KDIGO	39.3	10.2	Hospital 90 days	25.6 33.7	NS	-	3.7	NS	-
[47]	624	Surgical	RIFLE	58	8	Hospital 1 year	19 35	4 14	+15 +21	ICU: 6 Hospital: 19	ICU: 3 Hospital: 9	+3 +10
[48]	274	RRT	RIFLE	All	All	ICU Hospital	58.4 62	-	-	ICU: 14 Hospital: 22	-	-
[49]	182	Post-partum	Cr≥ 89µmol/ RIFLE	37.3	28	NS	NS	NS	-	4	2	+2
[50]	1,769	GP	AKIN	28.9	NS	30 days 1 year	13.3 28.8	6.0 16.5	+7.3 +12.3	NS	NS	-
[51]	40	GP	RIFLE	75	NS	ICU	30	10	+20	NS	NS	-
[52]	1,070	GP	RIFLE	Men: 35.8 Women: 38.7 Both: 37.3	NS	NS	NS	NS	-	NS	NS	-
[53]	445	GP	KDIGO	48.8	33.2	90 days	15.3	NS	-	(±) 4.3	2.1	2.2
[54]	27	MV	RIFLE	All	NS	ICU	44.4	NS	-	NS	NS	-
[55]	3,350	GP	RIFLE/ AKIN	21 21.1	NS	ICU	46.5 47	NS	-	NS	NS	-

*Note: Only articles published between January 2013 and February 2017. Abbreviations: AKIN - Acute Kidney Injury Network; AKIN-m - AKIN modified; CIAI - complicated intra-abdominal infection; CIN – Contrast-induced nephropathy; ClCr – Clearence of creatinine; Cr - Creatinine; Cys-C - Cystatin C; DC - Developed countries; Diff. - Simple difference between patients with and without AKI; EC - Emerging countries; GP - General population; HIV - Human Immunodeficiency Virus; KDIGO - Kidney Disease Improving: Global Outcomes; MV – Mechanical ventilation; NS - Not specified; Ref - Reference; RIFLE - Risk, Injury, Failure, Loss, End-stage kidney disease; RRT – Renal replacement therapy; sCr-a – Serum creatinine adjusted to the water balance; SOFA – Sequential Organ Failure Assessment; UO – Urine Output; V+P – Vancomycin with piperacillin-tazobactam; V+C – Vancomycin with cefepime.

increases linearly with age, as well as the chance of needing RRT, which further increases the mortality rate of patients.[1,2,14,17,24]

Almost all studies listed in Table 1 present diabetes mellitus and systemic arterial hypertension as the chronic diseases that are the most prevalent risk factors in critically ill adults with AKI. Moreover, these are also the chronic conditions that frequently increase morbidity and mortality for AKI in critically ill patients who are septic,[11,16,25] with fluid overload,[2,9,26] making use of nephrotoxic drugs[16] or who have undergone major surgeries.[7,8] Other chronic pathological conditions that are also noted as risk factors for AKI incidence and mortality in critically ill patients include cardiovascular,[9,17,27-30] respiratory,[10,31] cerebrovascular,[16] cirrhosis,[32,33] cancer[15,25], and human immunodeficiency virus infection.[10,34]

Several studies have shown baseline renal function as one of the most important risk factors for AKI. Luo et al.[35] performed prospective analysis of a database from Beijing (China), with more than three thousand adult patients, and observed that AKI patients identified by KDIGO criteria already had worse baseline renal function in comparison with those without AKI. In this same sense, Yokota et al.[24] in a prospective study with critically ill elderly patients verified that AKI patients presented worse baseline serum creatinine. Worse baseline renal function also was an AKI risk factor in the study performed by Wang et al.[36]

In others studies,[12,37-39] patients with AKI during ICU stay are the ones with higher serum creatinine at ICU admission, and in the studies performed by Podoll et al.[38] and Peres et al.[12] it was also associated with a higher risk for mortality.

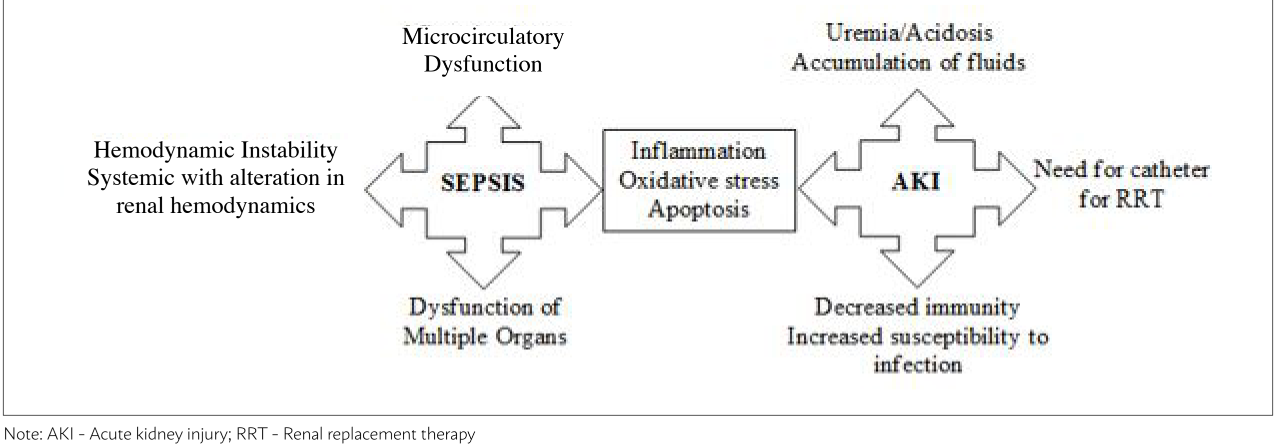
In the presence of sepsis, the reported incidence of AKI was greater than 70%, and mortality rate reached 80%, higher in patients undergoing RRT,[1,10,11,14,17,24,34,36,37,39-43] Sepsis was also an independent factor that increased the length of stay of individuals in ICUs.[11] The pathophysiological dynamics of the interaction between sepsis and AKI are not fully understood, and the association between sepsis and AKI in ICU patients can cause vascular, glomerular, tubular, and interstitial damage in the kidneys. Nevertheless, it is believed that the inflammatory process, oxidative stress, and apoptosis act as the link of the interaction between the events (see Figure 1). Vasodilation, hypoperfusion, and ischemic injury are probably the primary deleterious effects of this interaction.[3,5,11,20]

Nephrotoxic agents were an important factor contributing to AKI among critically ill patients[44]. Two recent studies have shown distinct results on the effect of contrast-induced nephropathy (CIN).[31,45] Hocine et al.[45] assessed 149 patients in a single-center study in Belgium and Kim et al.[31] 335 patients in the Republic of Korea. Although these studies showed a similar incidence of CIN, approximately 15%, CIN patients had a mortality rate 11% higher than those without CIN.[45] In another study, the ICU length of stay of patients with and without CIN was similar, nearly 15 days.[31] It should be noted that the pathophysiological genesis of CIN is not yet fully determined; however, the mechanisms may involve renal medullary ischemia and renal tubular damage by toxicity.[31,45]

Additionally, we verified that fluid overload might represent an independent risk factor for AKI development, need for RRT, and mortality.[9,26,32,36,44] Fluid overload can promote renal interstitial edema and consequent water and saline retention, increased interstitial pressure, reduction of renal blood flow and glomerular filtration rate.[26,32] Moreover, fluid overload is also a risk factor for increased intra-abdominal pressure, central venous pressure, and renal venous pressure, which contribute to worsening renal function.[26,32,36]

The use of diuretics in critically ill patients is frequent and one of the first strategies to minimize the consequences of fluid overload, but the administration may increase the risk of death in AKI patients.[37,46] In South America, the administration of diuretics was associated with higher mortality of critically ill AKI patients.[37] A multicenter Finnish study was identified in which 78.1% of patients who acquired AKI in the ICU were treated with vasoactive drugs.[46] In addition, the authors reported that over one-third of the AKI patients that used diuretics had hemodynamic stability or severe sepsis, and the use of diuretics was identified as a risk factor for the increase of AKI incidence.

FIGURE 1. PHYSIOPATHOLOGICAL INTERACTION BETWEEN SEPSIS AND AKI



Note: AKI - Acute kidney injury; RRT - Renal replacement therapy

In the United States, the combined therapy of vancomycin with piperacillin-tazobactam resulted in a higher AKI rate in ICU patients. However, no statistically significant differences were found regarding the need for RRT among patients taking vancomycin combined with cefepime.[16]

In a small prospective cohort, Nascimento et al.[7] evaluated 51 patients after bypass surgery and reported AKI incidence of 92.2%. In another study, the AKI occurrence was 5.2%, and the syndrome was an independent risk factor for myocardial injury.[8]

In addition to cardiac procedures, neurosurgeries, and transplants,[1] gastrointestinal, orthopedics, gynecological and urological surgeries[47] have also been associated with the occurrence of AKI in critically ill patients and are responsible for increasing the risk of death.

The RRT need can significantly increase both the length of hospital stay and patient mortality. In studies performed in Brasil, the mortality in patients undergoing RRT reached 58.4%[48] in the Southeast region and 84.2%[12] in the South region, and the mean length of hospital stay reached 36 days.[17] In two studies, the patients' mortality on continuous RRT modality was around 50%,[43,32] and in one study, the mortality in RRT by continuous and intermittent modalities reached 74.4%.[27]

There are studies in which the need for mechanical ventilation,[2,28,33] as well as elevated central venous pressure[30] and metabolic acidosis[28,42,45] have proved to be risk factors for AKI and death of patients who already presented the injury. Other risk factors are present in special populations such as patients with infectious diseases,[28] severe acute pancreatitis,[15] overweight/obesity,[32] obstetric complications,[49] malaria[42], and trauma victims.[38]

CONCLUSION

AKI incidence presented high variability among the studies, and the different criteria to define the cases is among the reasons. Availability of local resources, renal replacement therapy needs, serum creatinine at ICU admission, volume overload, and sepsis, among others, influence the mortality rates in AKI patients. This literature review demonstrated that a varied combination of risk factors are linked to the increasing incidence and persistence of high mortality rates in the ICU. We believe that knowing the epidemiological aspects of AKI and identifying its main risk factors to achieve early diagnosis are the first steps toward enhancing patient outcomes.

Declaration of Conflicting Interests

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Highlights

The incidence of AKI in critically ill patients is worrisome, regardless of geographical location;

The value of serum creatinine when the patient is admitted to the ICU can help the early diagnosis of AKI;

Sepsis persists with the cause-effect role of AKI, showing a strong association both to the incidence and to the increased mortality of critically ill patients;

Requiring RRT continues to have a relationship with worse outcomes;

Reducing preventable cases and deaths is a challenge to be faced by all health staffs.

Author Contributions

Passoni dos Santos R contributed with (1) the conception and design of the work, the acquisition, analysis, and interpretation of the data, (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Carvalho ARS contributed with (1) drafting the article and revising it critically for important intellectual content; (2) final approval of the version to be submitted.

Peres LAB contributed with (1) the conception and design of the work, the acquisition, analysis, and interpretation of the data, (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted.

Ronco C and Macedo E contributed with (1) drafting the article and revising it critically for important intellectual content; (2) final approval of the version to be submitted.

RESUMO

INTRODUÇÃO: *Injúria renal aguda (IRA) é um evento frequente entre pacientes criticamente enfermos internados em unidade de terapia intensiva (UTI) e representa um problema de saúde pública global, sendo imperativa uma abordagem interdisciplinar.*

OBJETIVO: *Investigar, por meio de revisão de literatura, a epidemiologia da IRA em UTIs.*

MÉTODOS: *Pesquisa on-line nas bases de dados Medline, Scientific Electronic Library Online e Literatura Latino-americana e do Caribe em Ciências da Saúde, com análise dos 47 estudos de maior relevância publicados entre 2010 e 2017.*

RESULTADOS: *Foram analisados dados de 67.033 pacientes, internados em mais de 300 UTIs de diferentes regiões do mundo. A incidência global de IRA variou de 2,5% a 92,2% e a mortalidade, entre 5% e 80%. O tempo de internação em UTI variou de cinco a 21 dias, enquanto que a necessidade de terapia renal substitutiva, de 0,8% a 59,2%. Pacientes com IRA apresentam índice de mortalidade substancialmente maior e tempo de internação mais elevado, em comparação com pacientes sem IRA.*

CONCLUSÃO: *A incidência de IRA apresentou alta variabilidade entre os estudos e, dentre os motivos, estão os diferentes critérios utilizados para definição dos casos. Disponibilidade de recursos locais, necessidade de terapia renal substitutiva, creatinina na admissão na UTI, sobrecarga volêmica e sepse, dentre outros, influenciam as taxas de mortalidade entre os pacientes com IRA.*

PALAVRAS-CHAVE: *Lesão renal aguda. Unidades de terapia intensiva. Epidemiologia. Fatores de risco.*

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