Risk factors for acute renal injury in intensive clinical patients

Fatores de risco para lesão renal aguda em pacientes clínicos intensivos

Factores de riesgo para lesión renal aguda en pacientes clínicos intensivos

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How to cite:
Benichel CR, Meneguin S. Risk factors for acute renal injury in intensive clinical patients. Acta Paul Enferm. 2020;33:e-APE20190064

DOI
http://dx.doi.org/10.37689/acta-ape/2020A00064

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Keywords
Acute kidney injury; Risk factors; Critical care; Inpatients;

Descritores
Lesão renal aguda; Fatores de risco; Cuidados intensivos; Pacientes internados

Descriptores
Lesión renal aguda; Factores de riesgo; Cuidados críticos; Pacientes internos

Submitted
March 20, 2019

Accepted
March 14, 2019

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Abstract

Objective: Identify the prevalence and associated factors of acute renal injury in intensive clinical patients and compare them with a control group; analyze if the coexistence of factors serves as a predictor for the risk of developing acute renal injury.

Method: Case-control study with a quantitative approach, developed at a general adult intensive care unity in the interior of São Paulo, Brazil, involving 205 patients who developed acute renal injury and the same number of controls, during 2014 and 2015. Data were collected through a survey of patient file records. Relationships were statistically significant if $p<0.05$.

Results: The prevalence of acute renal injury was 7.5% and the main associated factors were: arterial hypertension (p=0.004; OR=1.9615; CI=1.0491-3.6645); hypovolemia (p=0.006; OR=5.6071; CI=1.6382-19.1854); heart failure (p=0.003; OR=5.3123; CI=1.7521-16.1051); noradrenaline (p<0.0001; OR=9.4913; CI=4.4824-20.0981); dopamine (p=0.0009; OR=3.5212; CI=1.6701-7.4242); dobutamine (p=0.0131; OR=5.2612; CI=1.4172-19.5323); and simultaneous antibiotics (p<0.0001; OR=3.7881; CI=2.0253-7.0884). The coexistence of more than three risk factors was statistically significant for acute renal injury (p<0.0001; OR=5.0074; CI=2.5601-9.7936).

Conclusion: Acute renal injury is a multifactorial event associated with the baseline disease, the complications deriving from the severity of the patients' condition and the use of nephrotoxic drugs. Having three or more risk factors increased the chances for the development of the disease.

Resumo

Objetivo: Identificar prevalência e fatores associados à lesão renal aguda em pacientes clínicos intensivos, e compará-los com um grupo controle; analisar se a coexistência de fatores constitui preditor de risco para o desenvolvimento de lesão renal aguda.

Métodos: Estudo caso-controle, com abordagem quantitativa, realizado em unidade de terapia intensiva geral adulto do interior de São Paulo, Brasil, com 205 pacientes que desenvolveram lesão renal aguda e o mesmo número de controles, durante os anos de 2014 e 2015. Coleta de dados realizada mediante levantamento dos registros de prontuário. Relações foram estatisticamente significativas se p<0,05.

Resultados: A prevalência de lesão renal aguda foi de 7,5% e os principais fatores associados foram: hipertensão arterial (p=0,004; OR=1,9615; IC=1,0491-3,6645); hipovolemia (p=0,006; OR=5,6071; IC=1,6382-19,1854); insuficiência cardíaca (p=0,003; OR=5,3123; IC=1,7521-16,1051); noradrenalina (p<0,0001; OR=9,4913; IC=4,4824-20,0981); dopamina (p=0,0009; OR=3,5212; IC=1,6701-7,4242); dobutamina (p=0,0131; OR=5,2612; IC=1,4172-19,5323); e antibióticos simultâneos (p<0,0001;

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Conflicts of interest: none to declare.

OR=3,7881; IC=2,0253-7,0884). A coexistência de mais de três fatores de risco foi estatisticamente significante para lesão renal aguda (p<0,0001; OR=5,0074; IC=2,5601-9,7936).

Conclusão: A lesão renal aguda é um evento multifatorial que se associou à doença de base, às complicações decorrentes da gravidade dos participantes e à utilização de medicamentos nefrotóxicos. Ter três ou mais fatores de risco aumentou as chances para o desenvolvimento da doença.

Resumen

Objetivo: Identificar prevalencia y factores asociados a la lesión renal aguda en pacientes clínicos intensivos y compararlos con un grupo de control; analizar si la coexistencia de factores constituye predictor de riesgo para el desarrollo de lesión renal aguda.

Métodos: Estudio caso-control, con enfoque cuantitativo, realizado en unidad de cuidados intensivos general adulto del interior del estado de São Paulo, Brasil, con 205 pacientes que desarrollaron lesión renal aguda y el mismo número de controles, durante los años 2014 y 2015. Recolección de datos realizada mediante recopilación de registros de historia clínica. Relaciones fueron estadísticamente significativas si p<0,05.

Resultados: La prevalencia de lesión renal aguda fue de 7,5% y los principales factores asociados fueron: hipertensión arterial (p=0,004; OR=1,9615; IC=1,0491-3,6645); hipovolemia (p=0,006; OR=5,6071; IC=1,6382-19,1854); insuficiencia cardíaca (p=0,003; OR=5,3123; IC=1,7521-16,1051); noradrenalina (p<0,0001; OR=9,4913; IC=4,4824-20,0981); dopamina (p=0,0009; OR=3,5212; IC=1,6701-7,4242); dobutamina (p=0,0131; OR=5,2612; IC=1,4172-19,5323); y antibióticos simultáneos (p<0,0001; OR=3,7881; IC=2,0253-7,0884). La coexistencia de más de tres factores de riesgo fue estadísticamente significante para la lesión renal aguda (p<0,0001; OR=5,0074; IC=2,5601-9,7936).

Conclusión: La lesión renal aguda es un evento multifactorial que se asoció a la enfermedad de base, a las complicaciones resultantes de la gravedad de los participantes y a la utilización de medicamentos nefrotóxicos. Tener tres o más factores de riesgo aumentó las chances de desarrollo de la enfermedad.

Introduction

Acute Renal Injury (ARI) is a systemic, multifactorial condition that contributes to the increased morbidity and mortality rates of patients hospitalized at Intensive Care Units (ICUs).[1] In hospitals, it is one of the most frequent complications in inpatients, with prevalence ranges between 15 and 30%, a rate that almost doubles in ICUs.[2] It is estimated that 13% of the patients at these units will receive renal replacement therapy, 50 to 60% of whom will die.[2,3]

Among the risk factors for the development of ARI, preexisting clinical conditions and therapeutic interventions stand out, besides individual susceptibility, which can influence the kidney function. The aging process is also related, linked to chronic-degenerative illnesses and morphofunctional renal disorders.[4]

The early diagnosis of ARI is directly related with a better prognosis for critical clinical patients. Commonly used strategies include the measuring of biological markers, based on the analysis of laboratory data, which signal acute changes that interfere in the kidney function.[5,6]

In addition, and in view of the need to better standardize the criteria used in the different studies, the expert group of the *Acute Dialysis Quality Initiative* (ADQI) established the RIFLE criterion: risk (R), injury (I), failure (F), loss (L) and end-stage kidney disease (E); later, experts from the *Acute Kidney Injury Network* (AKIN) published a new ARI classification for adults, considered as an evolution of RIFLE. Finally, the guidelines of the *Kidney Disease Improving Global Outcomes* (KDIGO), published in 2012, incorporate the RIFLE and AKIN criteria, characterizing ARI by an increase of three tenths of milligrams (0.3 mg/dL) or more per deciliter of serum creatinine in 48 hours, or by one and a half in relation to the known or preestablished baseline level or assumed within the past seven days, or a urinary flow inferior to half a milliliter per kilogram per hour(0.5mL/kg/h) for six hours.[6,7]

Based on the premise that ARI worsens the prognosis of ICU patients and that prevention and early treatment strategies guarantee a better evolution of the clinical condition,[1-3] the role of a specialized multiprofessional team is fundamental to minimize complications and start the appropriate treatment for each case early in the intensive care context.

The nursing team needs emphasis, being the main provider of specialized assistance. Nurses play a substantial role in the prevention of ARI in ICUs. When in possession of qualified knowledge, they act on the different complexities and complications the treatment or the intrinsic conditions of critical clinical patients trigger. Through systemized conducts, they contribute to the reduction of problems and the early detection of worsening in the kidney function.[8,9] The nursing diagnosis permits differen-

tiated care, supporting the decision-taking process on the situations to improve the multiprofessional care, as care for ARI patients should be a priority to promote their safety.[10]

Nevertheless, despite the complexity and severity of the theme, little discussion is found in the nursing literature and few studies compare ARI patients with the respective controls in order to justify the results found. That is the gap in which this research was performed, aiming to answer the following questions: what factors are associated with ARI in critical clinical patients? Is there a difference in the factors associated with critical inpatients when compared to a control group? Does the coexistence of risk factors serve as a predictor of ARI in ICU? What is the prevalence of ARI? In view of the above, this study aimed to identify the prevalence and associated factors of ARI in intensive clinical patients and compare them with a control group; and analyze if the coexistence of factors serves as a predictor for the risk of developing ARI.

Method

An exploratory and retrospective case-control study with a quantitative approach was undertaken. The study took place at a general adult ICU of a private hospital in the interior of São Paulo, Brazil, offering up to 28 beds for patients from prehospital care, emergency care, surgical center, hemodynamics, diagnostic centers and inpatient units. During the research period, 20 beds were active, distributed between clinical and surgical care.

A non-probabilistic sample was constituted, including patients who developed ARI and were hospitalized at the service in 2014 and 2015.

For the cases, patients were considered eligible if 18 years or older, male and female, with an increase of 0.3 milligrams per deciliter (mg/dl) in the baseline serum creatinine levels durign the first 48 hours of ICU hospitalization, according to the definition adopted in the KDIGO classification, adopting the creatinine criterion.

Baseline creatinine was considered as the most recent level determined by the institution's laboratory measure, before the ICU hospitalization, between 30 days and six months from the admission date to the service. For those patients without an earlier creatinine test, the first level collected upon the patient's hospital admissions was considered and also, when not available, the first level collected after the ICU hospitalization. Patients with chronic renal disease documented in the patient history and cases of rehospitalization were excluded.

Only the creatinine criterion was adopted to stratify the patients, keeping in mind that the urinary flow is a dynamic variable, influenced by countless clinical and hemodynamic factors.

In addition, as controls, patients were included who were hospitalized at the ICU during the research period and did not develop ARI. The case patients were paired up with the controls using the case patients' mean age (±SD) as a criterion. The control sample was defined in function of the number of cases identified during the study period. The case patients who developed ARI were included in the "ARI" group, while the controls constituted the "No ARI" group.

The researcher collected the data between January and November 2016 by consulting the patients' electronic history, using two computer systems: *Phostos* and *MedWiew*. Using these tools and applying some search filters, a list of hospitalizations was obtained, which contained the name, file number and care register.

Next, the laboratory test result system called *Lhaudos* was consulted to identify the availability of serum creatinine data. Then, the inclusion and exclusion criteria were checked, as well as the finding of ARI according to the KDIGO criterion.

For both groups, a six-part form was used to collect the data: patient identification data (sex, age, color, marital status, days of hospitalization), hospitalization variables (days of hospitalization, deployment of the hospitalization, use of mechanical ventilation, entry diagnosis), antecedents and/or clinical conditions (cardiovascular risk factors and other comorbidities, nephrological risk factors), procedures performed (vascular and contrasted), nephrotoxic drugs/antibiotics use and laboratory tests.

As nephrotoxic drugs, the use of furosemide, non-steroidal or hormonal anti-inflammatory agent, angiotension-converting enzyme inhibitors, chemotherapeutic and antibiotic drugs, classified as: β-lactamases, quinolones, glycopeptides, lipopeptides, polypeptides, oxazolidinones, aminoglycosides, macrolides, lincosamides, sulfonamides, nitroimidazoles, antiviral and antifungal drugs.[11-16]

Based on the inclusion criteria, 205 patients were selected who developed ARI during the research period and the same number of controls.

In this study, the quantitative variables, such as age and monitoring time at the institution, were analyzed as means and standard deviations.

The other, qualifying variables, such as sex, color, marital status, entry diagnosis, outcomes, associated factors (cardiovascular, nephrological, comorbidities and drugs) and laboratory results were presented in tables with absolute (n) and relative (%) frequencies.

The statistical analysis was developed in two stages, using SPSS 21. Statistically significant variables in the univariate analysis($p<0.20$) and reported in the literature as potential risk factors for ARI were used to adjust the multiple logistic regression model. P-values <0.05 (95% confidence interval) were considered statistically significant.

In the second stage, the double-interaction test was applied between the exposures included in the multiple model. The final model only considered the main effects of each exposure which, in this stage, sustained an association value to predict the increased chance in view of the dependent variable, based on the knowledge of the relation with a group of independent variables that are considered statistically significant. This produced an odds ratio of ARI among critical clinical patients.

Approval for the study was obtained from the Ethics Committee of Botucatu Medical School under opinion 1.246.910 and CAE 48567315.2.0000.5411.

Results

Based on the inclusion criteria, 410 patients were selected for the study sample, with 205 patients in each group. In Table 1, the participants' sociodemographic characteristics are displayed. Most participants were female with 210 patients (51.2%), 221 had a partner (53.9%) and 354 (86.3%) were Caucasian. Concerning the entry diagnoses, respiratory 118 (28.8%) and cardiovascular 106 (25.9%) diagnoses stood out in both groups with a statistically significant difference ($p=0.0178$ and $p=0.0008$, respectively). It was also verified that the percentage of participants who used mechanical ventilation was higher in the ARI group, with 127 (61.9%). In the same group, the mean length of hospitalization was also higher 9.8 days (SD±10.2 days), both with statistical significance ($p<0.0001$). Practically half 96 (46.8%) were classified as stage I renal problems and death 136 (66.4%) was the significant outcome in this group ($p<0.0001$). The prevalence of ARI was estimated at 7.5%.

In Table 2, the data on the logistic regression analysis of the statistically significant variables for the development of ARI in patients from the ARI group are shown. Among the baseline conditions, arterial hypertension ($p=0.0349$; OR=1.9615; CI=1.0491-3.6645); and heart failure ($p=0.0032$; OR=5.3123; CI=1.7521-16.1051) stood out as risk factors for ARI, increasing by almost two and more than five times the chances of developing the disease, respectively. Hemodynamic conditions associated with hypovolemia increased the chances of ARI fivefold ($p=0.0060$; OR=5.6071; CI=1.6382-19.1854). As for the potentially nephrotoxic drugs the participants used, it was observed that the use of noradrenaline ($p<0.0001$; OR=9.4913; CI=4.4824-20.0981); dopamine ($p=0.0009$; OR=5.2612; CI=1.6701-7.4242); dobutamine ($p=0.0131$; OR=5.2612; CI=1.4172-19.5323) and simultaneous antibiotics ($p<0.0001$; OR=3.7881; CI=2.0253-7.0884) increased the participants' chances of developing ARI nine-, three-, five- and fourfold, respectively.

In Table 3, the coexistence of factors associated with the development of ARI is described. Most participants in the ARI group (59.5%) presented more than three coexisting factors during the ICU stay in the research period, which contributed to the participants' fivefold higher chance of developing ARI ($p<0.0001$; OR=5.0074; CI=2.5601-9.7936).

Table 1. Sociodemographic and clinical variables and deployments of the study participants' hospitalization

Variables	ARI n(%)	No ARI n(%)	Total n(%)	*p-value*
Age (years)*	74.6(15.5)	72.4(13.8)	73.5(14.7)	0.1784
Days of hospitalization*	9.8(10.2)	4.6(6.1)	7.2(8.7)	0.0001
Sex				
Female	102(49.8)	108(52.7)	210(51.2)	0.5538
Male	103(50.2)	97(47.3)	200(48.8)	
Marital status				
With partner	107(52.2)	114(55.6)	221(53.9)	0.4885
No partner	98(47.8)	91(44.4)	189(46.1)	
Ethnic origin				
Caucasian	182(88.8)	172(83.9)	354(86.3)	0.1509
Non Caucasian	23(11.2)	33(16.1)	56(13.7)	
Entry diagnoses				
Cardiovascular				
Yes	38(18.5)	68(33.2)	106(25.9)	0.0008
No	167(81.5)	137(66.8)	304(74.1)	
Gastrointestinal				
Yes	32(15.6)	23(11.2)	55(13.4)	0.1951
No	173(84.4)	182(88.8)	355(86.6)	
Neurological				
Yes	30(14.6)	40(19.5)	70(17.1)	0.1918
No	175(85.4)	165(80.5)	340(82.9)	
Respiratory				
Yes	70(34.1)	48(23.4)	118(28.8)	0.0178
No	135(65.9)	157(76.6)	292(71.2)	
Trauma / Orthopedics				
Yes	4(2.0)	6(2.9)	10(2.4)	0.5250
No	201(98.0)	199(97.1)	400(97.6)	
Urinary				
Yes	22(10.7)	12(5.9)	34(8.3)	0.0737
No	183(89.3)	193(94.1)	376(91.7)	
Others				
Yes	9(4.4)	8(3.9)	17(4.2)	0.8367
No	196(95.6)	197(96.1)	393(95.8)	
Use mechanical ventilation				
Yes	127(61.9)	25(12.2)	152(37.1)	0.0001
No	78(38.1)	180(87.8)	258(62.9)	
KDIGO classification				
I	96(46.8)	-	-	-
II	71(34.7)			
III	38(18.5)	-	-	-
Deployments of the hospitalization				
Death	136(66.4)	29(14.2)	165(40.3)	0.0001

* Mean (Standard Deviation); KDIGO – Kidney Disease Improving Global Outcomes

Table 2. Logistic regression of risk factors for ARI in critical clinical patients

Variables	Odds Ratio	CI (95%)		*p-value*
Arterial hypertension	1.9615	1.0491	3.6645	0.0349
Hypovolemia	5.6071	1.6382	19.1854	0.0060
Heart failure	5.3123	1.7521	16.1051	0.0032
Noradrenaline	9.4913	4.4824	20.0981	0.0001
Dopamine	3.5212	1.6701	7.4242	0.0009
Dobutamine	5.2612	1.4172	19.5323	0.0131
Two or more simultaneous antibiotics	3.7881	2.0253	7.0884	0.0001

CI – confidence interval

Table 3. Coexisting risk factors of the study participants

Factors	ARI n(%)	No ARI n(%)	Total n(%)	Odds Odds Ratio	CI (95%)		p-value
> 3	122(59.5)	21(10.2)	143(34.9)	5.0074	2.5601	9.7936	0.0001

CI – confidence interval

Discussion

The study results permitted the identification of the main factors associated with ARI, besides contributing to reflections on the importance of multiprofessional care provision, especially of nursing care, in the prevention and control of complications for ICU patients.

In addition, it can contribute to support care practice through the elaboration of care protocols for the early detection and monitoring of the evolution of ARI in clinical patients.

As a limitation, the research development at a single private hospital is highlighted. Furthermore, the lack of registers in the electronic patient history was observed, as well as the absence of a patient severity score and the non-use of standardized scales in the literature, with a view to the identification of ARI.

Participants of high age, Caucasians and individuals with a partner also stood out. These data find support in other studies that showed higher renal injury rates among patients with a mean age over 70 years[4] and with the same racial characteristic.[5]

As regards the outcomes, the length of hospitalization and death were significant events. The extended ICU stay can negatively affect the health condition, increasing the risk of complications and mortality, as demonstrated in recent studies.[2,5,8,9] In addition, an association is observed between the ARI progression, increased clinical deterioration and the severity [2] score, a condition directly related with the worsening of the prognosis and death. In addition, it should be taken into account that, when the renal condition becomes stratified, like in the KDIGO proposal, the patients' complexity becomes clearer than in the staging of the nephropathy they experience.[7,8]

The high mortality identified in this study clarifies the need for better care to this population, also identifying the main risk groups for the sake

of monitoring, early detection and adoption of preventive measures.

In addition, the length of ICU hospitalization, as from five days, in addition to the need for mechanical ventilation and emergency surgery, increases the risk for the development of severe conditions, including the deterioration of the renal function.[17] The mean length of the ARI patients' stay in this study was approximately ten days.

Concerning the entry diagnoses, respiratory conditions stood out as the main motive associated with the development of ARI among the investigated patients. This fact probably contributed to the dependence on ventilation and the other complication deriving from the extended hospitalization. In a prospective cohort involving 27 patients at a public hospital, ventilation therapies were associated with changes in the cardiac output and in the glomerular filtration rhythm, mainly when higher positive end-expiratory pressure is used.[17]

According to the analyzed data, practically half of the participants with ARI suffered from KDIGO stage I renal problems, in line with data from a retrospective study involving 157 critical patients[18] and a cohort of 2.719 patients.[19] Other studies also demonstrate variations among the classifications, mainly when the maximum degree of the dysfunction is analyzed, as evidenced in a study of clinical profiles and the relation with severe infection processes, in which high percentages of KDIGO II and III were found.[19] It is emphasized that, at the institution where the research was carried out, the use of this scale is not part of the institutional routine. Nevertheless, to guarantee the methodological rigor of the research, the researchers undertook this case-by-case survey.

To answer the second research objective, the logistic regression of the patients who developed ARI was undertaken, and of the control group without ARI, adopting some explanatory variables. Among the cardiovascular risk factors, arterial hypertension and congestive heart failure stood out as statistically significant. This was confirmed in a study involving 37 severely ill patients, whose factors were described as coadjuvants of the renal impairment.[20] Arterial hypertension and diabetes are considered the main factors associated with the development of ARI.[1,2,10,18] In addition, the occurrence of hemodynamic changes, associated with hypovolemia, and the use of nephrotoxic agents also significantly contributed to ARI in this investigation.

In this study, the antibiotics therapy quadrupled the chances of renal problems, mainly among the patients who used these drugs simultaneously, that is, more than one class of antibiotics at the same time. Among the main classes that entail risks for the development of ARI, aminoglycosides,[13] glicopeptides and polimixins[6,20,21] have been confirmed in the literature.

In a coadjuvant role to the nephrotoxic potential, vasoactive drugs were also associated with the development of ARI among the study participants. In a retrospective study, in which the files of 74 patients were analyzed, the use of these drugs prevailed among the participants with renal problems and death risk, showing a significant association with higher severity and mortality. In addition, the use of vasoactive drugs is one of the possible causes of renal injury, mainly when used concomitantly with other nephrotoxic agents.[5]

The nephrotoxicity is due to the vasoconstrictive effect that indirectly causes ischemia, with a consequent reduction of the renal blood flow. Caution is due with the harmful effects, whether due to the doses or the extended usage.[5] This condition requires constant surveillance, mainly monitoring the renal function through urea, creatinine and urinary output dosing.[7,8]

In this study, despite the statistically significant risk factors for the development of ARI, the prevalence was relatively low when compared to other studies, in which the renal dysfunction ranged between 23 and 53%.[2,10,18,19,,21] This percentage was only similar to that in this study in a retrospective research (8%).[13] It should be taken into account that the lack of a standardized ARI diagnosis among the consulted publications directly influenced the identified prevalence rates and therefore limited its classification.

In this research, almost 60% of the participants in the ARI group presented more than three coexisting factors, which contributed to increase the risk of renal dysfunction more than fivefold. On the other hand, the coexistence of the risk factors is hardly explored in the literature and, when mentioned, the data presented are related to the combination of some factors, like in a retrospective study[13] on the use of vancomycin and nephrotoxic drugs, also considering the combination of these factors with the combined use of other antibiotics and radiological contrast fluid.

It is emphasized that, when coexistent, the associated factors cause a greater impact on the renal problem,[2,4,5] and that the ARI results from the synergy of intrinsic and extrinsic factors, a condition that influences the prognosis of critical clinical patients.[8,12,19]

Conclusion

In critical clinical patients, ARI is a multifactorial event, which notably happens in patients of advanced age, with a longer hospitalization period, a predisposes to death. It was associated with the baseline disease, the complications deriving from the severity of the patients' condition and the use of nephrotoxic drugs. The prevalence was low when compared to the literature. In addition, the study also showed that the coexistence of more than three risk factors contributed to the development of ARI.

Collaborations

Benichel CR declares that he contributed to the project design, data analysis and interpretation, writing of the article and relevant critical review of the intellectual content and final approval of the version for publication. Meneguin S declares that she contributed to the project design, data analysis and interpretation, writing of the article and relevant critical review of the intellectual content and final approval of the version for publication.

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