

REVISTA CIÊNCIAS EM SAÚDE



HEALTH SCIENCES JOURNAL e-ISSN 2236-3785

ORIGINAL ARTICLE

Evaluation of prediction score of contrast-induced nephropathy in inpatients undergone to digital or CT angiography

Avaliação de escore de predição de nefropatia induzida por contraste em pacientes submetidos a angiografia digital ou angiotomografia computadorizada

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Received 25 Apr 2020; accepted 30 Aug 2020; published online 11 Sep 2020

KEYWORDS Digital subtraction angiography Computed tomography angiography Contrast media Renal insufficiency Risk factors

ABSTRACT

Objectives: To assess the incidence of contrast-induced nephropathy (CIN) and determine the Mehran Score's (MS) ability to predict CIN in patients undergoing digital angiography or computed tomography angiography. **Methods:** 252 medical records of inpatients who underwent DA or CTA over 28 months in a quaternary hospital were reviewed. CIN was defined as serum creatinine > 0.5 mg/dL or > 25% increase in baseline creatinine, 48 h after administration of iodinated contrast. The

Roc curve and the area under the curve (AUC) were used as a score test. **Results:** The majority (159; 63.1%) were male, and the average age was 60.4 years. Anemia, diabetes mellitus, and age > 75 years were the most prevalent factors. The incidence of CIN was 17.8% (n = 45). There was a decrease in the mean values of creatinine pre and post among patients who did not suffer CIN (1.38 \pm 1.22 vs 1.19 \pm 0.89; t = 3.433; p = 0.0007), while among patients who suffering CIN, the mean increase was 1.03 mg / dL

 $(1.43 \pm 1.48 \text{ vs } 2.46 \pm 2.35 \text{ mg} / \text{dL}; t = 5.44; p = 0.117)$. The ROC curve analysis identified a low correlation between MS and the occurrence of CIN (AUC = 0.506). **Conclusion**: The incidence of CIN in hospitalized patients undergoing angiography or computed tomography angiography was high. The EM did not allow the prediction of NIC.

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This study was carried out at Itajubá Clinics Hospital

https://doi.org/10.21876/rcshci.v10i3.974

How to cite this article: Jesus-Silva SG, Chaves AE, Maciel CAA, Scotini EEF, Mesquita PGM, Moraes-Silva MA, et al. Evaluation of prediction score of contrast-induced nephropathy in inpatients undergone to digital or CT angiography. Rev Cienc Saude. 2020;10(3):78-84. https://doi.org/10.21876/rcshci.v10i3.974

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PALAVRAS-CHAVE Angiografia digital Angiografia por tomografia computadorizada Fatores de risco Insuficiência renal Meios de contraste

RESUMO

Objetivos: Avaliar a incidência de nefropatia induzida por contraste (NIC) e determinar a capacidade do Escore de Mehran (EM) em prever a NIC em pacientes submetidos à angiografia digital ou angiotomografia.

Métodos: Foram revisados 252 prontuários de pacientes internados submetidos à AD ou ATC no período de 28 meses em hospital quaternário. A NIC foi definida como creatinina sérica > 0,5 mg/dL ou um aumento > 25% da creatinina basal, 48 h após a administração do contraste iodado. A curva ROC e a área sob a curva (ASC) foram utilizadas como teste do escore.

Resultados: A maioria (n = 159; 63,1%) era do sexo masculino e a média de idade foi de 60,4 anos. Anemia, diabetes melito e idade > 75 anos foram os fatores mais prevalentes. A incidência de NIC foi de 17,8% (n = 45). Houve diminuição nos valores médios da creatinina pré e pós entre os pacientes que não sofreram NIC (1,38 \pm 1,22 vs 1,19 \pm 0,89; t = 3,433; p = 0,0007), enquanto dentre os pacientes que sofrerem NIC, o aumento médio foi de 1,03 mg/dL (1,43 \pm 1,48 vs 2,46 \pm 2,35 mg/dL; t = 5,44; p = 0,117). A análise pela curva ROC identificou baixa correlação entre o EM e a ocorrência de NIC (ASC = 0,506).

Conclusão: A incidência de NIC em pacientes internados submetidos à angiografia ou à angiotomografia foi elevada. O EM não foi capaz de predizer a NIC.

INTRODUCTION

Contrast-induced nephropathy (CIN) is a known cause of acute renal failure in a hospital environment due to the broad indication of the use of iodinated contrast to performing radiological examinations, such as digital angiography (DA) (peripheral arteriographies or coronary angiography) and helical computed tomography angiography (CTA)¹⁻³. CIN is most commonly defined as an absolute increase in serum creatinine equal to or greater than 0.5 mg/dL (44.2 mmol/L) or a relative increase of 25% or more in the baseline, which occurs in the absence of another etiology, after 48 or 72 h of contrast exposure³.

CIN is considered a reversible and benign disease that resolves within approximately one week³. However, it can damage the patient's renal function, both in the long and in the short term, being able to prolong hospitalization, attend to the need for temporary or permanent dialysis, and increase hospital mortality^{3,4}. Minimizing contrast administration, using iso-osmolar or low-osmolarity iodinated contrasts, and establishing a renal preparation with previous and continued volume expansion for hours after the procedure are generally effective in preventing CIN^{2,5}.

However, in some patients, even a minimal amount of contrast can lead to CIN, especially in those hospitalized and who have other associated risk factors, such as dehydration, infections, postoperative status, and ICU stay⁵⁻⁷. The incidence of CIN is less than 5% in patients without risk factors. However, it is increased in patients with any comorbidity that may result in reduced renal plasma flow, such as chronic kidney disease (CKD), diabetes mellitus (DM), diabetic nephropathy, advanced age, congestive heart failure (CHF) and hypovolemia. The use of nephrotoxic drugs, patients who had previously undergone diagnostic tests, and excessive volume of contrast are also related to CIN's increased incidence, reaching up to 50% in those with multiple risk factors^{8,9}.

Renal dysfunction caused by radiocontrast is a potentially severe complication of angiographies, diagnostic or interventional. In general, it is estimated

that up to 5% of patients undergoing coronary angiography may have at least a transient elevation of creatinine^{10,11}. Furthermore, since there is no specific treatment for CIN, prevention is the best way to deal with this condition.

A thorough risk assessment carried out before percutaneous coronary intervention and adopting a prophylactic regimen is the key to preventing CIN¹²⁻¹⁴. The Mehran Score (MS) was developed and initially validated to predict CIN after angiography and/or coronary angioplasty. This score includes eight clinical and procedural variables with their appropriate scores: systemic arterial hypotension (five points), CHF (five points), age over 75 years (four points), use of an intraaortic balloon pump (five points), baseline serum creatinine > 1.5 mg/dL or creatinine clearance < 60 mL/min/1.73 m² (four points), DM (three points), anemia (four points) and contrast volume used (one point for each 100 mL). The risk score distribution is divided into four risk classes for the CIN, as shown in Table 1^{11,15}.

It is not clear, however, whether MS can be appropriately used in cases of individuals hospitalized and undergoing peripheral DA or CTA, in addition to coronary angiogram. It is possible that, even in these cases, MS is as predictive in predicting CIN as in the case of coronary angiographies. The present study, therefore, aims to determine the incidence of CIN and to verify the positive and negative predictive values of MS in hospitalized patients undergoing diagnostic or interventional procedures in a quaternary hospital.

Table 1 - Risk classes for contrast-induced nephropath	y
(CIN), according to the Mehran Score ¹ .	

Risk Class	Risk score	CIN risk	Dialysis risk
Low	≤ 5	7.5%	0.04%
Moderate	6 a 10	14.0%	0.12%
High	11 a 16	26.1%	1.09%
Very High	≥16	57.3%	12.6%

METHODS

A retrospective study was carried out by analyzing the medical records of 252 patients who underwent iodinated contrast in helical CTA exams (at the Diagnostic Medicine Service) or diagnostic or interventional DA (at the cath lab) at Itajubá Clinics Hospital, Minas Gerais, Brazil. The DA data refer to exams carried out between March 2016 and September 2017, while the CTA data, from March to December 2019, totaling 28 months. The study was approved by the Research Ethics Committee of the Faculty of Medicine of Itajubá, under decision number 2,900,955.

The sample was calculated based on an expected incidence of CIN of 6%8,10 in a low-risk, infinite dimensional population, with a 95% confidence level, and a maximum error of 3%, obtaining 241 individuals. Data were collected from 252 patients, with a 5% loss of medical record information expected. The sampling was consecutive and not randomized in both periods of collection. We included all those who underwent CTA or DA exams, regardless of age, who remained in the intensive care unit or conventional inpatient units (wards or apartments) for at least 48 h after the exam, and who had serum creatinine pre and post administration of the contrast. Medical records that were considered incomplete, whose MS parameters were not fully noted, or if serum creatinine were collected less than two or more than three days after the exam, were excluded. All iodized contrast used was non-ionic with low osmolality (iohexol, Omnipaque 300 or 350 mg/mL, GE Healthcare®, Shanghai, China). A specific protocol for CIN's prophylaxis was not instituted in hospitalized patients, since they were already in parenteral hydration. Acetylcysteine was not used in any patient studied.

CIN was defined as an increase in serum creatinine above 0.5 mg/dL or above 25% from baseline. A spreadsheet data collection instrument that contained eight variables was developed: presence or absence of DM, CHF, systemic arterial hypotension during the examination, anemia, use of an intra-aortic balloon, age greater than 75 years, serum creatinine before the procedure and 48 h after, according to what is recommended in the MS.

Anemia was defined as a hematocrit of less than 39% for men and 36% for women. CHF was considered in individuals with cardiac dysfunction with a confirmed diagnosis of grade III/IV CHF according to the New York Heart Association classification or history of pulmonary edema. Systemic arterial hypotension was defined in patients with a systolic blood pressure of 80 mmHg or less during the procedure for at least one hour, requiring inotropic support with drugs and/or intraaortic balloon pump (IABP) within the first 24 h after the procedure. DM was defined using established clinical criteria for diagnosis and classification, such as a fasting blood glucose > 126 mg/dL, or postprandial blood glucose > 200 mg/dL, or chronic use of hypoglycemic agents.

The data were tabulated in an electronic spreadsheet. Descriptive statistics were performed using means and standard deviations or absolute and relative frequencies, depending on the variables.

Inferential analysis was performed using Student t-test or Fisher's exact test for variables with normal or dichotomous distribution. The diagnostic test analysis was done by calculating sensitivity, specificity, positive predictive value, and negative predictive value and by the ROC curve (Receiver Operating Characteristics), with the calculation of the Area Under Curve (AUC). Those whose values were in the low and medium risk classes (score \leq 10) and those with high and very high risk (score \geq 11) were arbitrarily considered "negative" and "positive" MS. Graphpad Prism v.8 software (San Diego, California, USA) was used, with a 95% confidence interval and statistical significance as p < 0.05.

RESULTS

Of the 252 patients studied, 159 (63.1%) were male, and 93 (36.9%) were female. The mean age was 60.4 ± 17.7 years, ranging from 11 to 94 years. Figure 1 shows the sample's histogram of age. Sixty-seven patients (26.6%) underwent cardiac procedures, 55 (21.8%) peripheral DA and 130 (51.6%) computerized CTA. The average contrast volume of the sample was 125.5 \pm 51.4 mL (DA: 166.7 \pm 58 mL, 95%CI 146.9 - 186.5 mL; CTA 109.5 \pm 32 mL, 95%CI 105, 6 - 113.5 mL; p <0.0001). The MS average for the total sample was 6.75 (95%CI 6.21 - 7.30). Table 2 shows the frequencies of the MS variables present and the incidence of CIN in the sample.



Figure 1 - Histogram of the age of the 252 patients admitted to the Itajubá Clinics Hospital and evaluated for the occurrence of CIN. Most cases were between the fifth and seventh decades of life.

A decrease in the mean of serum creatinine before and after the procedure was observed among patients who did not present CIN ($1.38 \pm 1.22 \text{ mg/dL} \text{ vs. } 1.19 \pm$ 0.89 mg/dL; t = 3.433; p = 0.0007). Among patients suffering from CIN, the mean increase was 1.03 mg/dL($1.43 \pm 1.48 \text{ mg} / \text{dL} \text{ vs. } 2.46 \pm 2.35 \text{ mg/dL}$; t = 5.44; p < 0.0001). Figure 2 illustrates the variation in serum creatinine values before and after the procedure for the sample.

Table 2 - Variables of the Mehran score and incidence of contrast-induced nephropathy observed in the sample (N = 252).

Variables	n (%)
Anemia	150 (59.5)
DM	60 (23.8)
Age > 75 years	52 (21)
Pre serum creatinine > 1.5 mg/dL	45 (17.9)
CHF	28 (11.1)
Systemic arterial hypotension	11 (4.4)
Contrast volume (mL) average (SD)	125.5 (51.5)
Intra-aortic balloon pump	-
Pulmonary edema	-

CIN 45 (17.8) DM, diabetes mellitus CHF; congestive heart failure; CIN,

contrast-induced nephropathy; SD, standard-deviation.

The stratification of each risk group and the distribution of CIN's incidence for each group is shown in Table 3. It is possible to observe a high incidence of CIN in the high-risk group (32% of 25 patients) and the low and moderate risk groups (17.4 and 15%,

respectively). The comparison between the observed risk factors in the groups with and without CIN is detailed in Table 4. It was not possible to observe statistically significant differences between the two groups of patients concerning the MS variables. It was possible to obtain values related to sensitivity, specificity, and positive and negative predictive values of MS concerning CIN's occurrence, described in Table 5.

The ability to predict NIC by MS was obtained by calculating ASC on the ROC graph of sensitivity versus specificity. ASC was 0.506 (95% CI: 0.413 to 0.599; p = 0.89) (Figure 3).

Table 3 - Distribution of the sample in relation to the stratification of risk groups according to Mehran Score and the relative incidence of contrast-induced nephropathy (CIN) (N = 252).

Risk group	Sample (%)	CIN (%)	Without CIN (%)
Low	138 (54.8)	24 (17.4)	114 (82.6)
Moderate	80 (31.7)	12 (15)	68 (85)
High	25 (19.9)	8 (32)	17 (68)
Very high	9 (3.6)	1 (11.1)	8 (88.9)

Table 4 - (Comparison	between	the f	frequency	of	Mehran	Score	risk	factors	present	in	the	group
with and wi	ithout CIN.												

Risk factors	CIN (%)	Without CIN (%)	p-value	
Systemic arterial hypotension	2 (4.4)	9 (4.3)	> 0.99*	
CHF	4 (8.9)	24 (11.6)	0.79*	
Age > 75 years	7 (15.5)	46 (22.2)	0.42*	
Anemia	26 (57.8)	124 (59.9)	0.86*	
DM	15 (33.3)	45 (21.8)	0.12*	
Contrast volume - mL (SD)	123 (49)	135 (59)	0.20†	
Pre serum creatinine > 1.5 mg/dL	8 (17.8)	37 (17.9)	> 0.99*	

*Fisher's exact test; †Student t test for independent samples; SD, standard deviation.

Table 5 - Sensitivity, specificity and positive and negative predictive values of the Mehran score for NIC, after arbitrary cutoff point (low and moderate risks vs. high and very high risks), in the sample (N = 252).

Score characteristics	Value (%)	95% CI
Sensibility	20.0	10.9 - 33.8
Specificity	87.9	82.8 - 91.7
Positive predictive value	26.5	14.6 - 43.1
Negative predictive value	83.5	78.0 - 87.8

DISCUSSION

The present study identified a high incidence of CIN in the sample of hospitalized patients, in addition to not identifying the adequacy of MS as a predictor of renal dysfunction. Such findings speak in favor of the fact that MS may not be useful as a predictor of CIN in all cases.

CIN is a major cause of renal failure in the hospital environment, corresponding to the third cause of acute dysfunction, with 11% of cases¹⁶. It is diagnosed several times after invasive or non-invasive diagnostic procedures, as shown in the present study. The occurrence of contrast-induced kidney injury ends up



Figure 2 - Boxplots of the distribution of serum creatinine values before and after contrast administration, according to the evolution or not for contrast-induced nephropathy in the sample (n = 252). Student t test for dependent samples.



Figure 3 - ROC curve for evaluating of Mehran Score. The low AUC value (0.506; 95% CI 0.412 - 0.599; p = 0.898) indicates that the model did not adequately correlate with the clinical findings of CIN for the analyzed sample.

prolonging the patient's hospitalization period, leading to clinical complications and increased hospital mortality at the time of the event, maintaining an extended risk for up to five years of follow-up and representing an increase in costs for the institution^{14,15,17}.

CIN ranges from less than 1% in the general population and up to 50% in high-risk patients, leading to a more extended hospital stay, cost of maintenance, and substantial mortality and morbidity⁸. Following the definition criteria presented above, 17.8% of patients in the present study developed CIN, representing a larger number than those usually found in the literature, as previously mentioned^{1,18}. Among the risk factors, it is noteworthy that most individuals had anemia, which may indicate clinical decompensation.

However, it was impossible to determine whether this anemia was due to acute blood loss or chronic disease.

Considering the possible prognostic indicators of CIN, given the main risk factors for its occurrence, the risk stratification score for the disease was developed in 2004 by Mehran and collaborators. In the study, 4,989 patients were compared with a control group of 2,786 individuals to define a classification system to predict the risk of CIN after percutaneous coronary angioplasty. Those who had a severe shock and acute myocardial infarction with pump failure were excluded from the study^{1,19}. Stratification is based on the analysis of variables of patient-related characteristics (age over 75 years, DM, chronic heart disease, systemic arterial hypotension, anemia and CKD) and the procedure (use of contrast and volume)⁹.

It should be noted that the group that did not develop CIN (88% of the sample) actually showed an improvement in the mean serum creatinine value. It is possible that, even after the supply of iodinated contrast, standard hydration measures in hospitalized patients are essential for improving renal function. Comparing the frequency of risk factors between those who developed and did not develop CIN did not show a statistically significant difference between the groups, which goes against similar studies²⁰.

Despite efforts to prevent or mitigate CIN, such as the use of beta-blockers or acetylcysteine⁵, recent studies have spoken against these drugs²¹. The use of vasoconstrictor and nephrotoxic drugs significantly contribute to renal dysfunction, even without the additional contribution of iodinated contrast. In any case, CIN's primary preventive measure continues to be hydration with saline before the use of contrast and, preferably, for hours, a measure that is impossible to be performed in emergency cases, for example, in an acute heart attack¹⁰.

Based on an arbitrary division of high and low risk to develop CIN, reduced values of sensitivity and positive predictive value were obtained regarding the characteristics of the score. In contrast, the values of specificity and negative predictive value were reasonably high. It is possible to conclude that the MS, in the analyzed sample, was adequate to define which individuals would have a low probability of developing CIN. Other studies in patients specifically destined for coronary/valve intervention showed closer sensitivity and specificity values (62 and 68%, respectively)²⁰. Therefore, it is inferred that MS has a more remarkable ability to predict CIN in exclusive groups of patients undergoing cardiac intervention than in general patients undergoing non-invasive imaging exams²².

The calculation of the area under the curve in a ROC is a usual mechanism for testing prediction scores, and the low result for assessing MS obtained in the present study indicates that the model did not correlate adequately with the clinical findings of CIN for the analyzed sample. A previously mentioned study obtained a reduced AUC (0.654; 95% CI 0.495 - 0.758)²⁰. New scores are developed in order to simplify the assessment and, at the same time, maintain a capacity to predict CIN reasonably²³.

Among the study's limitations, we can mention the unicentric nature, a sample limited to the intention of

describing a prevalence, the absence of comparison between groups, and the fact that blood samples could have been collected outside the recommended time interval. Also, different groups of contrasted tests (DA and CTA) were simultaneously included in the analysis. This association may have been fundamental to the unfavorable results of MS in forecasting CIN. It is also possible to mention the short follow-up within 48 hours of the contrast administration, which prevents the diagnosis and monitoring in the hospital or at home.

New studies must try not to associate different, complementary exams in the analysis, to provide further homogeneity to the sample. However, we consider the study valid, as it allowed accurate knowledge of the CIN rate in hospitalized patients and

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repelled MS as an applicable tool in the prediction of acute kidney injury in all patients.

CONCLUSION

The incidence of CIN in hospitalized patients undergoing digital angiography or computed tomography angiography was low. There was no association with any risk factor for MS in the occurrence of CIN. The score used was of little use in predicting the occurrence of kidney injury, despite having an excellent ability to predict low-risk cases due to its greater specificity and negative predictive value.

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Conflicts of interest: No conflicts of interest declared concerning the publication of this article.

Indications about the contributions of each author:

Conception and design of the study: AEC, PGMM, CAAM, EEFS, SGJS Analysis and interpretation of data: AEC, CAAM, EEFS, SGJS Data collection: AEC, CAAM, EEFS Writing of the manuscript: AEC, CAAM Critical revision of the article: MAMS, SGJS, RSC Final approval of the manuscript*: AEC, CAAM, EEFS, PGMM, MAMS, RSC, SGJS Statistical analysis: SGJS Overall responsibility: SGJS *All authors have read and approved of the final version of the article submitted to Rev Cienc Saude.

Funding information: Not applicable.