COMSERVA:
Jurnal Penelitian dan Pengabdian Masyarakat
Volume 4 No. 8 Desember 2024 (XXX-XXX)
e-ISSN: 2798-5210
p-ISSN: 2798-5652

The NGAL Serum Level in Patient with Contrast-Induced Nephropathy (CIN): A Systematic Review and Meta-Analysis

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DOI:10.59141/comserva.v4i8.2714

ABSTRACT

Contrast media are commonly injected into the bloodstream to increase image contrast and improve the diagnostic capabilities of radiological examinations. Contrast-induced nephropathy (CIN) is a severe complication of renal impairment after administration of contrast media. NGAL is a reliable early biomarker that has been studied in contrast to kidney damage and other conditions that affect the kidney. This study aimed to determine the mean difference in serum NGAL levels between patients with and non-CIN which will be used as the cutoff value for predicting CIN. The search was performed using three databases with the following eligibility criteria: (1) adult patients (> 18 years old), (2) patients who underwent the procedure with contrast medium injection, and (3) diagnosis of CIN based on the increase in serum creatinine level after contrast infusion. Meta-analysis was performed using a random-effect model. The mean difference (MD) and confidence interval of serum NGAL (ng/mL) between CIN and non-CIN after contrast media injection based on nine studies (1,293 subjects) was 84.14 (95% CI: 48.90, 119.38) ng/mL. Egger's regression test showed significant asymmetry in the funnel plot (p < .0001). This study found a positive difference in serum NGAL levels between patients with and without CIN after contrast medium injection.

Keywords: *CIN, contrast media, NGAL, kidney disease.*

INTRODUCTION

In recent years, contrast media have been commonly injected into the bloodstream to increase the image contrast and improve the diagnostic capabilities of radiology examination (Li & Wang, 2024)(Ozkok & Ozkok, 2017). However, the complication of using contrast media should be considered, including contrast-induced nephropathy. Contrast-induced nephropathy (CIN) is a severe complication of renal impairment after administration of contrast media (Shams & Mayrovitz, 2021). CIN is defined as an increase in serum creatinine (SCr) by > 25% or an increase of ≥ 0.5 mg/dL from the baseline level, 24-48 hours post after contrast media administration (Mamoulakis et al., 2017). A recent meta-analysis of 259 articles showed that the pool effect estimates the incidence of CIN after contrast administration as high as 9.06% for angiography and 0.6% for dialysis (Wu et al., 2022). As the consequences, the occurrence of acute kidney injury (AKI) after contrast media injection (in the

case of coronary angiography) had increased rate of myocardial infarction (3.8%), bleeding (6.4%), and death (9.6%) if compared to non-AKI (Tsai et al., 2014).

The high incidence and morbidity of CIN, which worsened with an increase in the vulnerability to kidney disease among patients in this non-communicable disease era,8 should be countered by a specific biomarker to increase the diagnostic accuracy for CIN. In recent years, several biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), have been shown to increase during acute renal tubule events (Petrova et al., 2023) (Liao et al., 2019). NGAL is a reliable early biomarker that has been studied in contrast to kidney damage and other conditions that affect the kidney (Petrova et al., 2023) (Padhy et al., 2014). Several meta-analyses have analyzed the diagnostic and prognostic performance of NGAL in predicting or diagnosing CIN by NGAL measurement. However, there is no report on the specific level of NGAL (quantitatively) to determine the difference in mean NGAL serum levels between patients with and non-CIN after contrast media administration.12,13 This study aimed to determine the mean difference in serum NGAL levels between patients with and non-CIN which will be used as the cut-off value for predicting CIN before the creatinine serum increase–24-48 hours after contrast media administration.

METODE

The sources of the articles were based on four different databases and were registered as follows: (1) PubMed, (2) The Cochrane Library, and (3) Scopus. The search period was July – September 2024 . The search strategy was based on a population-exposure-comparison-outcome formulation. In this study, the population comprised adult patients, exposure was contrast-induced nephropathy (CIN), comparison was non-CIN, and the outcome was NGAL serum. The search strategy used to find relevant articles in this study was based on: ("contrast induced nephropathy") OR ("contrast induced nephropathy cin") AND ("ngal") AND ("neutrophil gelatinase associated lipocalin").

The inclusion criteria were as follows: (1) adult patients (> 18 years old), (2) patients who underwent the procedure with contrast media injection, and (3) diagnosis of CIN based on the increase in serum creatinine level after contrast infusion. The exclusion criteria were as follows: (1) comorbidities that caused alteration in NGAL concentration, (2) full text not available, and (3) publication not in English. The studies were progressively selected. Two reviewers will act as reviewers of the article to select the relevant studies independently with a progressive approach (relevant from title and abstract, deduplication, and full-text) based on eligibility criteria. The total number of studies relevant to the full text will be compared to each reviewer inserted into the Google Spreadsheet. If there are different perceptions among these reviewers, discussion and voting will be arranged for the other five reviewers. The data from the studies were collected from the metadata of Google Spreadsheets. The data collection was performed by two reviewers. There are no automated or artificial intelligence tools for collecting data from the selected studies. If there is a conflict between the two reviewers, a discussion and voting mechanism will be conducted by the other five reviewers. The outcome data from the selected studies were the mean NGAL serum levels between two different groups (CIN and non-CIN).

A certainty assessment of the summary of the study was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. This system evaluates the quality of the studies based on their study design, consistency of results, directness and precision of the evidence, and publication bias.

The risk of bias will be assessed using The Risk of Bias in Non-Randomized Studies – Of Exposure (ROBINS-E), which was used to assess the risk of bias in the systematic reviews of observational studies. The components assessed by this tool were as follows: (1) bias due to

confounding, (2) bias arising from measurement of the exposure, (3) bias in selection of participants into the study (or into the analysis), (4) bias due to post-exposure interventions, (5) bias due to missing data, (6) bias arising from measurement of the outcome, and (7) bias in selection of the reported result, to be accumulated as the overall bias.

Data Synthesis

Data will be synthesized by collecting data on the demographic status of the participants, followed by the collection of effect measures, which are the mean NGAL levels of CIN and non-CIN. Unavailable data on mean total serum ghrelin will be noted as N/A (not available) data and will not be included in the data analysis. The synthesis results are summarized in table. The meta-analysis will be performed for continuous data with a random-effect model (REM) using RStudio software to collect data on effect size, variance, heterogeneity, and publication bias that will be presented in a forest plot, funnel plot, and the measurement of funnel plot asymmetry with Egger's regression test.

RESULTS AND DISCUSSION

Study selection was performed using a progressive approach using three databases (PubMed, Cochrane Library, and Scopus). The PRISMA flow14 is as follows.

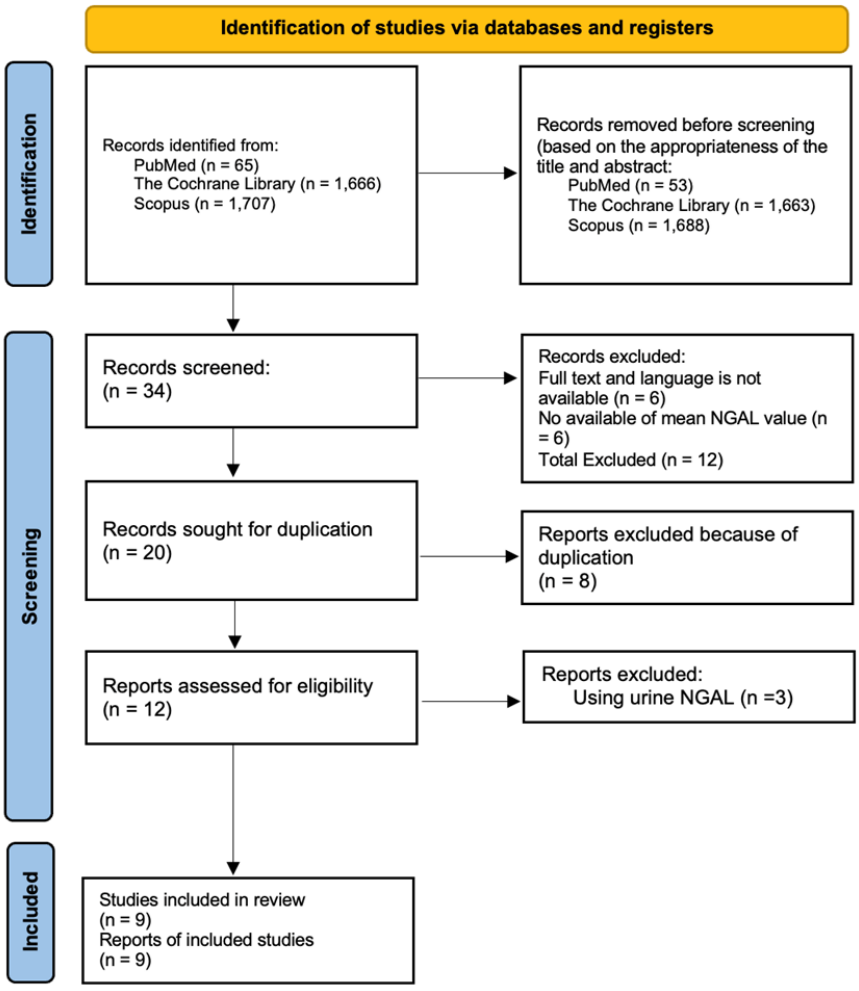

Figure 1. Study Selection Process

Table 1. Study Characteristics

Author (Year)	Subject's Characteristics	Number of Subjects	Method of Serum NGAL Measurement	Post Contrast Mean ± SD or Median of Serum NGAL (ng/mL)			
				CIN	SD or Median	Non-CIN	SD or Median
(Sahu et al., 2022)	• Single-center, prospective, observational study • Exclusion Criteria: - Had undergone coronary artery bypass surgery (CABG) within the past 1 month - Having an active infection, malignancy, and chronic inflammatory states	CIN (25) Non-CIN (187)	Triage® Alere™ NGAL test (ELISA)	400.6	269.3	109.8	68
(Alharazy et al., 2014)	Exclusion Criteria: - AKI - acute myocardial infarction - end-stage kidney disease - cardiogenic shock	CIN (11) Non-CIN (89)	ELISA kit R&D Systems (Minneapolis, Minnesota)	4h: 58.5 24h: 66.6	4h: 10.8 24h: 10.8	4h: 49.5 24h: 48.6	4h: 9.9 24h: 9.9
(Kafkas et al., 2016)	All adults (age >18 years) undergoing elective invasive cardiac procedures	CIN (33) Non-CIN (67)	ELISA	6h: 152.57 24h: 171.64 48h: 178.86	6h: 66.73 24h: 69.31 48h: 71.66	6h: 107.57 24h: 123.48 48h: 123.07	6h: 60.29 24h: 66.63 48h: 68.48
(Liao et al., 2019)	Exclusion Criteria: 1) patients with AKI caused by pre-renal, renal, or post-renal obstruction 2) patients using nephrotoxic drugs or contrast media within 2 weeks before surgery 3) patients with severe heart failure or other	CIN (25) Non-CIN (215)	ELISA	6h: 126.05 12h: 167.27 24h: 162.84 48h: 123.36	6h: 55.41 12h: 89.37 24h: 76.28 48h: 55.42	6h: 88.87 12h: 88.05 24h: 89.12 48h: 87.53	6h: 4.23 12h: 5.26 24h: 5.35 48h: 4.98

Author (Year)	Subject's Characteristics	Number of Subjects	Method of Serum NGAL Measurement	Post Contrast Mean ± SD or Median of Serum NGAL (ng/mL)			
				CIN	SD or Median	Non-CIN	SD or Median
	organ failures 4) patients with acute myocardial infarction 5) patients with acute infection						
(Luo et al., 2023)	Exclusion Criteria: (1) Patients with AKI caused by pre-renal, renal or postrenal obstruction (2) those who used nephrotoxic drugs or contrast media within 2 weeks before operation (3) those with severe heart failure or other organ failure (4) those with acute myocardial infarction (5) those with acute infection	CIN (25) Non-CIN (275)	ELISA	6h: 126.34 12h: 171.28 24h: 165.98 48h: 123.27	6h: 11.34 12h: 24.38 24h: 23.24 48h: 24.21	6h: 88.04 12h: 88.56 24h: 89.25 48h: 87.45	6h: 8.46 12h: 9.04 24h: 8.27 48h: 7.82
(Filiopoulos et al., 2013)	Exclusion Criteria: Pre-procedure SCr >150 μmol/L (1.7 mg/dL), overt congestive heart failure (stages III–IV according to New York Heart Association-NYHA functional classification system), haemodynamic instability of any cause, sepsis or systemic infectious disease	CIN (4) Non-CIN (43)	Standardized Triage® NGAL tes	779.25	361.49	82.3	40.64
(Guray et al., 2021)	Exclusion criteria: 1. New York Heart Association functional class IV 2. presentation of acute coronary syndrome, a recent history of the acute coronary syndrome within 3 months 3. basal serum creatinine level	CIN (16) Non-CIN (168)	Triage NGAL test	4h: 161 24h: 228.1	4h: 54 24h: 49.3	4h: 97.2 24h: 116.3	4h: 40.5 24h: 58.1

Author (Year)	Subject's Characteristics	Number of Subjects	Method of Serum NGAL Measurement	Post Contrast Mean ± SD or Median of Serum NGAL (ng/mL)			
				CIN	SD or Median	Non-CIN	SD or Median
	over 176.8 μmol/L or severe kidney dysfunction (estimated glomerular filtration rate [eGFR] below 0.5 mL/s/1.73 m2) 4. unstable hemodynamics 5. radiographic contrast media exposure within two weeks						
(Al Awady et al., 2022)	Exclusion criteria: 1. Patients with impaired renal functions (serum creatinine more than 1.3 mg/dl). 2. Refusal of participation in the study	CIN (4) Non-CIN (46)	N/A	409.5	55.91	167.36	24.25
(Padhy et al., 2014)	Exclusion criteria: 1) any pre-existing chronic nephropathy (serum creatinine > 1.2 mg/dl) including diabetic nephropathy 2) any systemic infection and urinary tract infection	CIN (30) Non-CIN (30)	ELISA	4h: 259.28 24h: 103.23 48h: 74.90	4h: 54.56 24h: 25.63 48h: 24.33	4h: 74.90 24h: 75.97 48h: 72.53	4h: 24.33 24h: 28.58 48h: 28.39

Risk of Bias in Studies

The risk of bias measured by ROBINS-E is shown in Figure 2.

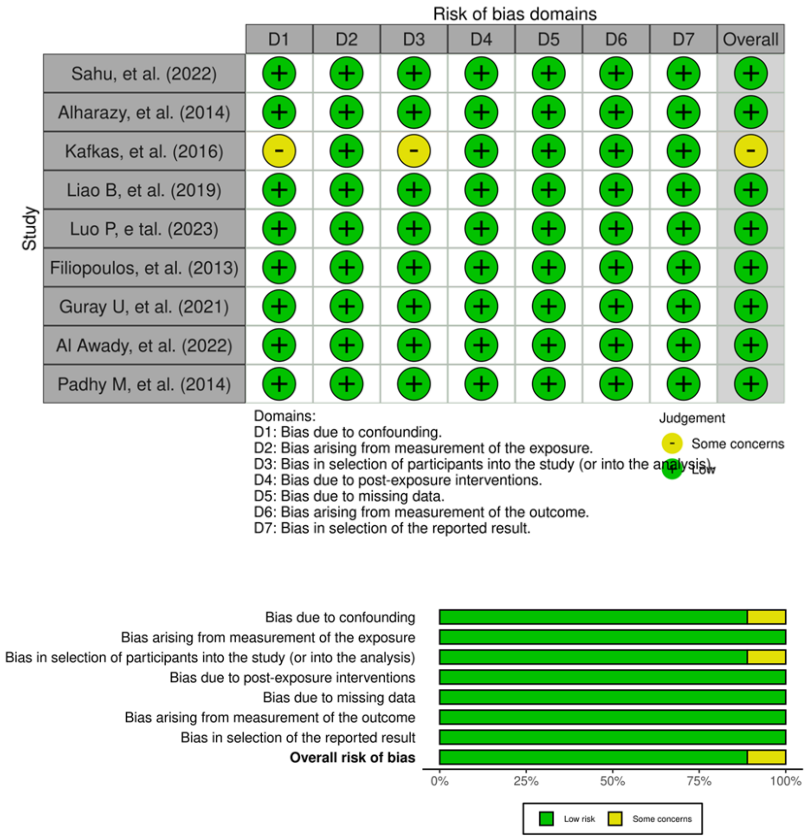

Figure 2. Risk of Bias Studies

Data Synthesis

The Mean Difference of Serum NGAL Level Between CIN vs Non-CIN After Contrast Media Injection. The mean difference (MD) and confidence interval of serum NGAL (ng/mL) between CIN and non-CIN after contrast media injection based on 9 studies (1,293 subjects) was 84.14 (95% CI: 48.90, 119.38) ng/mL (Figure 1).

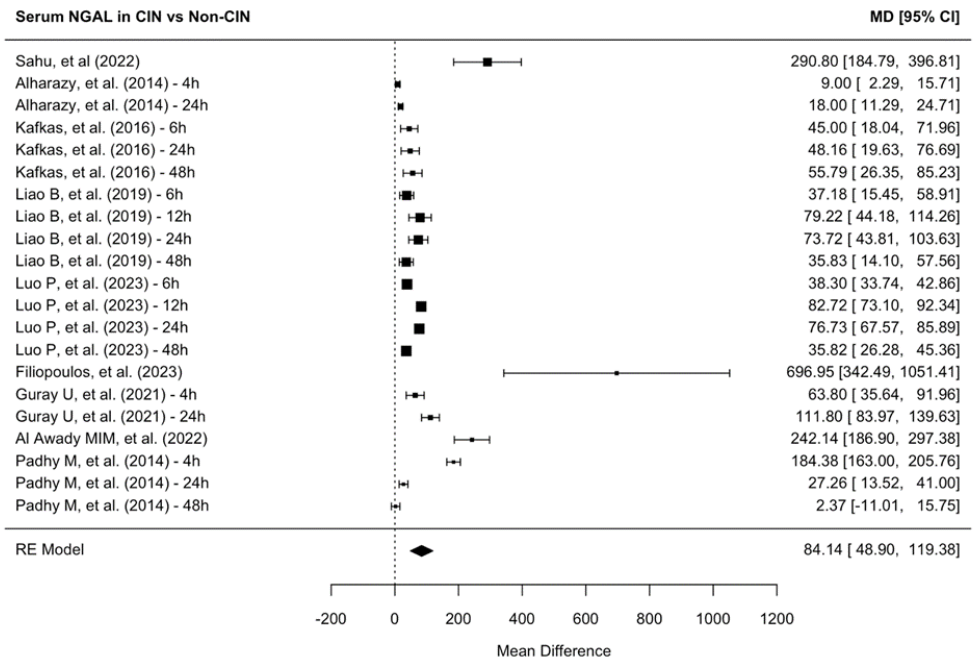

Figure 3. Forest Plot of NGAL Serum (ng/mL) Difference Between CIN and Non-CIN

Publication Bias

Publication bias was assessed using funnel plots; however, the heterogeneity of the 9 studies included in the analysis was very high, with an I2 of 99.04% and H2 of 104.53. Egger's regression test also showed significant asymmetry in the funnel plot ($p < .0001$).

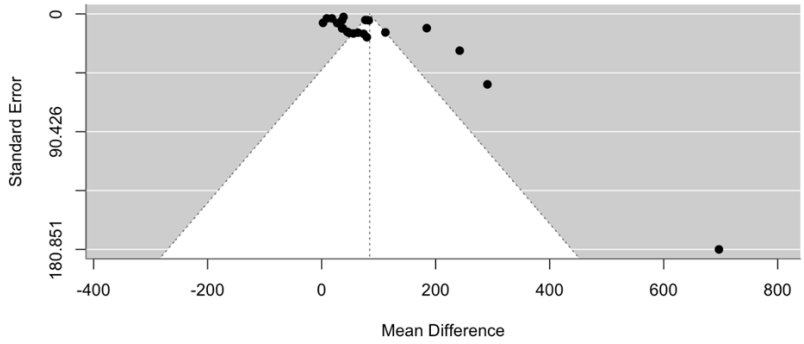

Figure 4. Funnel Plot of NGAL Serum (ng/mL) Difference Between CIN and Non-CIN

Discussion

From the meta-analysis with the random effects method, the mean difference (MD) of serum NGAL (ng/mL) between CIN and non-CIN after contrast media injection was 84.14 (95% CI: 48.90, 119.38) ng/mL). These positive findings were based on nine studies that included 1,293 subjects. This finding showed that serum NGAL levels were higher in patients with CIN than in those without CIN. Based on three studies (Alharazy, Guray, Padhy, et al.), CIN increases as early as 4 h after contrast administration. This indicates that NGAL can be used as a critical biomarker to detect or predict the probability of a patient undergoing contrast media procedures for CIN. This finding was supported by

the findings of Petrova et al., (2023) in 12 of 45 patients with CIN included in their study. This study showed that CIN patients had a higher increase in NGAL levels than subclinical CIN and non-CIN patients. The increase in NGAL started 4 h after contrast medium administration (Petrova et al., 2023).

However, basic knowledge of NGAL should be known for the use of this biomarker. NGAL or neutrophil gelatinase-associated lipocalin is a protein called lipocalin-2 (family of lipocalin proteins) that is mainly produced by neutrophils; however, this marker is also synthesized by other tissues, such as the kidney, lung, stomach, heart, epithelial cells, dendritic cells, and adipocytes. This protein had the ligand-binding site (calyx) that can facilitates the receptor attachment to the surface of membranes such as neutrophil chemoattractants (leukotrien B4 and the platelet-activating factor) (Al Jaberi et al., 2021; Romejko et al., 2023). In recent days, this marker can represent the renal tubular damage. This is caused by the process of kidney regeneration that requires iron and NGAL provides intracellular iron availability. Interestingly, serum NGAL levels also increase during kidney injury caused by neutrophil activation (Grigoryev et al., 2008; Romejko et al., 2023).

NGAL is also used for other indications besides predicting the risk of CIN. Reyes et al., (2020) observed serum NGAL levels and the requirement for hemodialysis in post-PCI patients. This study showed that serum NGAL can act as an early biomarker for detecting CIN and predicting the risk of hemodialysis requirements for the patient.27 Other reports states that the increase of NGAL also associated with the clinical stage and NYHA functional status of the patient with ischemic heart failure. In this recent years, NGAL also proposed to be used as the marker for myocardial infaction as the signiciant predictor for the adverse events (Lindberg et al., 2012; Vlachopoulos et al., 2015).

In this finding, even the results showed a positive difference in serum NGAL between CIN and non-CIN patients; however, this study has some limitations. The results of this study showed a high heterogeneity and funnel plot asymmetry. The high heterogeneity ($I2 = 99.04\%$ and $H2 = 104.53$) and significant funnel plot asymmetry (Egger's regression test with $P < 0.001$) may have been caused by the difference in the time of serum NGAL measurement from different studies, which caused the difference in the mean serum NGAL levels from every study. Future studies should use the exact time of serum NGAL measurements to determine the optimal time to measure serum NGAL levels.

Conclusion

This study concluded that there was a positive difference in serum NGAL levels between patients with and without CIN after contrast medium injection. However, the optimal time for serum NGAL measurement should be considered when evaluating and predicting the risk of CIN in patients undergoing contrast media procedures.

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