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Health Review

The Association Between Hematocrit Ratio and Outcomes in Kidney Transplantation: An Integrative Literature Review

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Abstract: With the increasing number of people affected by chronic diseases, such as chronic kidney disease, advances in treatments are being widely studied. Kidney transplantation is a commonly used curative measure when viable, and numerous studies focus on improving techniques and prognosis for both the patient and the graft. Recently, various cellular ratios have been applied and tested with the aim of clinically evaluating and estimating the likelihood of organ rejection after transplantation. The main one is the neutrophil-to-lymphocyte ratio (NLR), an effective, economical, and accessible measure for the practical clinical assessment of the degree of inflammation after kidney transplantation and, consequently, for predicting acute rejection (AR). The objective of this study was to search the literature for evidence regarding the behavior of cellular ratios and the status of kidney transplantation, investigating the association between the neutrophil-to-lymphocyte ratio and potential complications or outcomes in kidney transplantation. An integrative review was conducted through a bibliographic survey on the PubMed, Lilacs, and Scielo platforms between August 2023 and October 2024, selecting articles through pre-established filters related to the topic, such as cellular ratios and kidney transplantation, resulting in the final inclusion of six articles published between 2013 and 2024. Upon analyzing the results, it was evidenced that a high preoperative neutrophil-to-lymphocyte ratio (NLR > 3.5) may be considered a predictor for delayed graft function as well as the detection of acute rejection. This study aimed to contribute to advancements in kidney transplantation and assist in the early detection of post-transplant outcomes, given the importance of this treatment and the maintenance of a good prognosis for transplant patients. It also sought to encourage further research to better define the relevance and applicability of cellular ratio analysis, which is still underutilized in clinical practice, since there is no consensus regarding the sensitivity and specificity of this analysis for kidney transplantation outcomes and other clinical applications.

Keywords: Cellular Ratios; Neutrophil-to-Lymphocyte Ratio; Kidney Transplantation; Graft.

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1. Introduction

With the increase in life expectancy, the approaching inversion of the age pyramid, and the prevalence of unhealthy habits, chronic diseases have become increasingly prevalent and are gaining greater visibility due to rising incidence rates and the need for knowledge regarding their management and prevention [1]. Among these conditions is Chronic Kidney Disease (CKD), defined as heterogeneous renal alterations lasting three months or more, affecting both renal structure and function, and primarily characterized

by a reduction in glomerular filtration rate. CKD has become a significant public health issue both globally and in Brazil [2,3].

CKD has an insidious nature with multiple causes and prognostic factors, often remaining asymptomatic but leading to significant morbidity and mortality among patients. According to data from the International Organization World Kidney Day, 10% of the global population, approximately 850 million people, are affected by some degree of chronic kidney disease [4]. Brazil follows global prevalence patterns, showing progressive growth in the number of patients with advanced CKD. According to data from the Brazilian Society of Nephrology (SBN) Census in July 2020, the estimated total number of patients undergoing dialysis was 144,779 [18]. Additionally, studies have highlighted inequalities in access to treatment and a higher incidence of the disease in more vulnerable regions of the country, reflecting structural inequities [19].

In Brazil, CKD is also associated with risk factors such as sociodemographic conditions, unhealthy behaviors and lifestyles, and other chronic diseases [5,21,23]. Regional epidemiological profiles demonstrate variations in the clinical presentation of CKD, making the continuous analysis of these data essential for guiding public policies [20]. Due to the country's and the disease's heterogeneous nature, exact data are difficult to obtain; however, there is consensus both in Brazil and worldwide regarding the growing need for research, studies, and public campaigns addressing chronic kidney disease [5]. Furthermore, the mortality associated with CKD represents a public health challenge, as highlighted by recent integrative reviews that emphasize its increasing relevance in Brazil [22].

Renal replacement therapies are therapeutic procedures used either temporarily or permanently in situations where the kidneys lose their functionality and reduce their blood filtration capacity. They emerged to correct hydroelectrolytic imbalances, remove toxins, and, over the long term, improve survival, functional status, blood pressure control, and prevent uremic complications [6].

Renal replacement therapies can be classified as intermittent, continuous, or hybrid. Intermittent therapy includes conventional hemodialysis, involving extracorporeal blood clearance via vascular access, typically lasting 3 to 5 hours per session, three times a week. Continuous therapies include slow ultrafiltration, venovenous hemofiltration, venovenous hemodiafiltration, and slow venovenous hemodialysis, all involving sessions lasting longer than 12 hours, ensuring more thorough toxin filtration and more spaced treatment intervals. Alternatively, peritoneal dialysis uses the peritoneum's natural filtration capacity along with plasma osmolality to remove toxic substances. However, in cases of chronic renal failure, the definitive therapeutic solution is kidney transplantation, aiming to restore the organ's physiological functions [7].

Renal rejection is an immune response from the recipient's body (self) against the donor organ's cells (non-self) [8]. The reaction is based on cellular recognition through markers that act as antigens originating from the body itself or from external sources. The major histocompatibility complex (MHC) molecules are responsible for presenting non-self antigens to the immune system and determining histocompatibility between individuals based on the similarity between the recipient's and donor's MHC molecules. Depending on the timing, transplant type, and antibodies involved, rejection can be categorized as hyperacute, acute, or chronic. Advances in medicine have enabled better control of rejection processes through antibody detection and various immunosuppressive therapies [9].

Currently, various cellular ratios are being applied and tested with the objective of clinically evaluating and estimating the likelihood of organ rejection after transplantation. The most prominent among them is the neutrophil-to-lymphocyte ratio (NLR), an effective, economical, and accessible measure for the objective clinical evaluation of the degree of inflammation after kidney transplantation, which can consequently indicate the likelihood of acute rejection (AR) [7]. Several studies associate a high NLR with impaired graft function, meaning decreased and ineffective kidney function post-transplant [10].

NLR is also considered a general predictor of survival in patients who experience complications during hemodialysis [11]. Recent studies suggest that an elevated NLR in patients with end-stage renal disease is linked to an increased risk of cardiovascular complications.

Thus, this study aims to search the literature for evidence regarding the behavior of cellular ratios and the status of kidney transplantation, investigating the association between the neutrophil-to-lymphocyte ratio and possible complications or prognosis after kidney transplantation.

2. Materials and methods

In the present study, an integrative review was conducted. This type of research allows, based on evidence, the evaluation, synthesis, and acquisition of knowledge about a phenomenon, aiming to produce an overview of complex concepts, theories, or relevant health problems by synthesizing pre-existing studies, thus enabling the proposal of interventions. For the selection of articles, six methodological steps were followed: (1) formulation of the guiding research question or hypothesis, identifying the problem, search strategy, and descriptors or keywords; (2) establishment of inclusion and exclusion criteria for article selection; (3) exploratory reading of article titles and abstracts for pre-selection; (4) analytical reading of the articles to compile, analyze, and categorize the information; (5) interpretation of the results; and (6) synthesis followed by presentation of the results identified, addressing the guiding question.

Therefore, in this study, the search was focused on the following concepts: kidney transplantation, cellular ratios, prognosis, rejection, and renal replacement therapy. Based on these concepts, the guiding question was defined: what is the connection between the behavior of cellular ratios and the prognosis of kidney transplantation?

After formulating the research question, a bibliographic search was conducted using the PubMed, Lilacs, and Scielo platforms. The search was carried out between August 2023 and December 2023. The selection of texts proceeded through searches on these platforms, using available filters for articles published between 2013 and 2024. The inclusion criteria for publication selection were scientific articles published in English, Portuguese, or Spanish between 2013 and 2024, available online and in full for free. Articles without an abstract in the database, incomplete articles, editorials, letters to the editor, reflective studies, and systematic or integrative literature reviews were excluded.

After defining the guiding question, locating, and selecting the articles, 13 potentially eligible publications were identified. The abstracts of 8 records were analyzed, of which 2 were excluded due to thematic irrelevance, resulting in 6 articles included for full analysis, as shown in the selection flowchart.

3. Results and Discussion

Within the time frame defined for the execution of this study (2013–2024), six publications were found and analyzed. In 2013, one article was published (16.66%). In 2018, there were two publications (33.33%), and in 2019, two articles were published (33.33%). In 2022, one article was published (16.66%). According to the methodology of the selected works, the types of studies included prospective observational research, qualitative studies, and cross-sectional studies.

The publications came from different journals, namely: Transplantation Proceedings, Experimental and Clinical Transplantation, Medical Journal of Pokhara Academy of Health Sciences, and the Turkish Journal of Medical Sciences. Analyzing the study locations, one article was conducted in two countries, the United States and the United Kingdom (16.66%), one article in Japan (16.66%), one article in Poland (16.66%), one article in Nepal (16.66%), and two articles conducted in Turkey (33.33%).

Figura 1. Flowchart of article selection for integrative review.

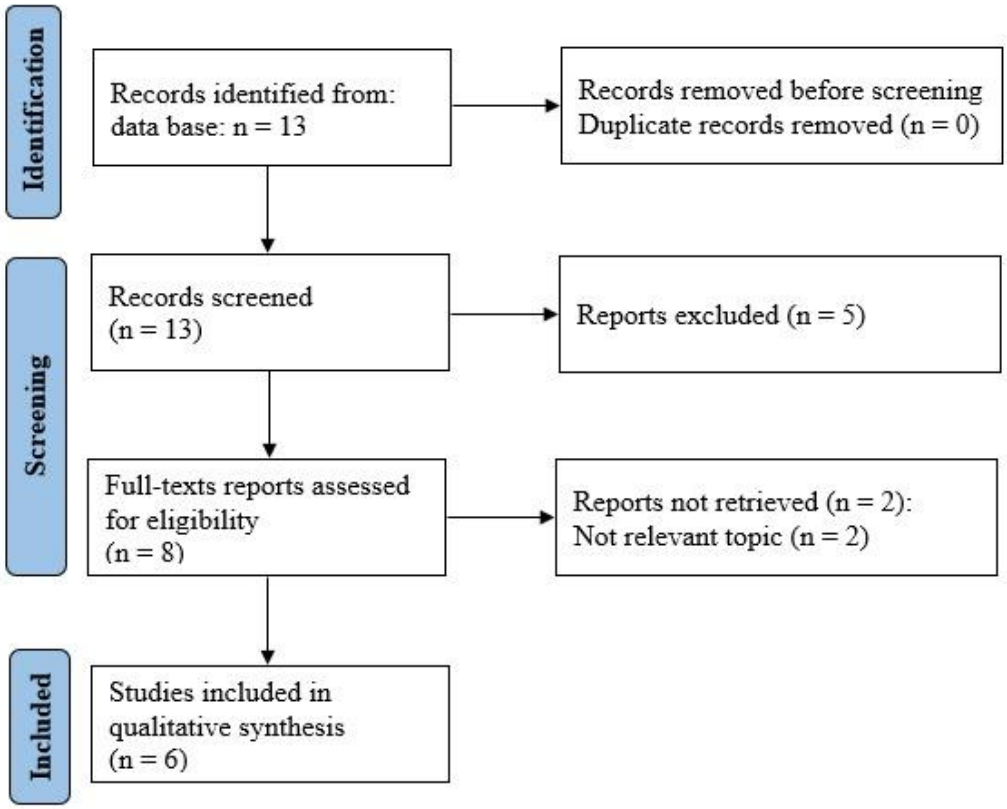

Table 1. Comparative synthesis of the studies included in the review.

Reference	Population	N (sample size)	NLR Cut-off	Main Outcomes	Sensitivity / Specificity
[12]	Adults	398	>3.5	DGF (Delayed Graft Function)	Not specified
[13]	Adults	137	Not defined	Post-transplant malignant tumors	Not specified
[14]	Adults	135	Not defined	eGFR <30, CRR2	NLR AUC = 0.664
[15]	Adults	298	>3.5	DGF	75.75% / 76.56%
[10]	Adults	51	>2.5	Acute rejection	Not specified
[16]	Pediatrics	51	<5	DGF	68.8% / 34.3%

In the study published by Halazun et al. [12], the authors sought to establish an association between an elevated neutrophil-to-lymphocyte ratio (NLR) and delayed graft function (DGF) in kidney transplantation. Based on this objective, the preoperative white blood cell count of kidney transplant recipients from 2003 to 2005 was retrospectively analyzed. A total of 398 transplant recipients were included and compared regarding gender, age, donor type, NLR value, complete blood count, and cold ischemia time (CIT)

of the graft. The comparison between the clinicopathological and demographic characteristics of patients with high and normal NLR showed statistically significant results for cold ischemia time greater than 15 hours (p=0.002) and for living donors (p=0.05). For the CIT variable, the relationship indicated that patients with a normal NLR exhibited longer CIT. As for the living donor (LD) variable, a significant number of patients with normal NLR were observed.

In the univariate analysis of factors, male sex (p=0.039), CIT greater than 15 hours (p<0.0001), preoperative NLR greater than 3.5 (p<0.0001), and donor type (p<0.006 and p<0.0001) significantly affected the development of DGF. In the multivariate analysis, elevated preoperative NLR (p<0.0001) and donor type (p=0.014 and p=0.024) were revealed as significant independent predictors for the development of DGF. Finally, it can be concluded that the individual analysis of NLR >3.5 shows specificity and sensitivity in predicting the risk of developing DGF. A CIT greater than 15 hours negatively impacts primary graft function, and donor type is also a modifying factor in future graft performance, particularly with living donors.

In the study by Ohtaka et al. [13], changes in the NLR after kidney transplantation and cases where malignant tumors developed post-transplant were analyzed. The study evaluated 137 patients who underwent kidney transplantation between August 2001 and September 2015, assessing NLR values. NLR was reported as an easily measurable tumor marker that can predict prognosis in some solid malignancies. Patients with higher NLR values exhibited worse prognoses. It was observed that NLR was markedly elevated one month after kidney transplantation and gradually decreased to stabilize three months post-transplant. In patients who died from malignant disease, the NLR continued to rise after transplantation. It was concluded that among patients who underwent transplantation combined with immunosuppressive therapy, there remains a percentage that progresses to malignant disease, demonstrating that the incidence of post-transplant malignancies has been increasing. Overall, it was observed that in most patients who developed malignant disease, the NLR rose over time, whereas in patients without malignant diseases, there was an increase in the first month followed by a significant decrease by the third month.

In the article by Hogendorf et al. [14], preoperative levels of monocytes, lymphocytes, platelets, and neutrophils and their ratios were retrospectively evaluated in a group of 135 kidney transplant recipients (from deceased donors, after brain death diagnosis, preserved in simple cold ischemia without mechanical perfusion). Statistically significant differences were observed between the groups with eGFR <30 (estimated glomerular filtration rate) and eGFR ≥30 in the mean values of lymphocytes (total lymphocyte count), NLR, LMR (lymphocyte-to-monocyte ratio), PLR (platelet-to-lymphocyte ratio), and CRR2 (creatinine reduction rate). In the univariate analysis, higher NLR, PLR, and CRR2 values were associated with better graft function, whereas higher lymphocyte counts and higher LMR values were associated with poorer graft function. Additionally, ROC curve analyses showed that lymphocytes and NLR were the strongest predictors of satisfactory and unsatisfactory graft function, respectively. The AUC was 0.636 for lymphocytes and 0.664 for NLR, indicating a moderate ability to distinguish between patients with eGFR ≥30 and eGFR <30.

In the univariate analysis, higher lymphocyte counts as well as lower NLR were associated with lower eGFR on the 21st day after kidney transplantation. The combination of lymphocytes, NLR, LMR, and CRR2 reduction correlated with serum creatinine levels on the 21st day and eGFR in transplant recipients, allowing early detection of recipients with poorer graft function in the early post-transplant period. In this study, it was reported that absolute lymphocyte count (ALC) and creatinine reduction between postoperative days 1 and 2 were the most important factors in predicting short-term graft function. Indeed, differences in NLR, PLR, and LMR between study groups were directly linked to differences in ALC. It was hypothesized that preoperative lymphocyte count monitoring could emerge as a useful factor in graft function evaluation. Furthermore, in

this clinical scenario, combining lymphocyte counts with CRR2 provided relatively high sensitivity, making the assessment of these factors even more promising.

In the study by Baral et al. [15], the authors sought to determine whether the evaluation of preoperative neutrophil-to-lymphocyte ratio (NLR) would be a better predictor of delayed graft function (DGF) in kidney transplants than the platelet-to-lymphocyte ratio (PLR). For this purpose, retrospective data was collected from 298 patients who underwent kidney transplantation between 2013 and 2016 from the institution's database. Recipients were compared regarding preoperative complete blood count, patient demographics, postoperative graft function, and cold ischemia time (CIT). From the blood count, NLR and PLR values were established, with elevated levels defined as NLR >3.5 and PLR >120. In the multivariate analysis of factors, NLR (p=0.000) and PLR (p=0.015) significantly affected the development of DGF. Thus, NLR >3.5 showed a sensitivity of 75.75% and specificity of 76.56% for predicting DGF, while PLR >120 demonstrated a sensitivity of 72.72% and specificity of 58.20% for the same outcome. Finally, it was concluded that NLR >3.5 is a sensitive risk factor for DGF. Although PLR also showed an association with DGF, it was less sensitive compared to NLR.

Regarding the analysis of the article by Ergin et al. [10], the author established a comparative relationship between NLR levels and the process of acute renal rejection using multivariate models. Through this retrospective study, data from 22 patients with biopsy-proven acute rejection and 29 control group patients were analyzed. It was demonstrated that increased NLR values (greater than 2.5) were statistically associated with acute rejection in kidney transplantation in the univariate analysis, leading to the conclusion that NLR could serve as a widely available and useful marker for detecting acute rejection in this patient population.

In the study by Siddiqui et al. [16], changes in NLR after kidney transplantation in children were demonstrated. The study included 51 pediatric patients who underwent kidney transplantation, comprising 33 males and 18 females, with a median age of 12 years. It was found that preoperative median lymphocyte counts were significantly higher in the group with delayed graft function (DGF) compared to the group without DGF (2 vs. 1 [p=0.040]). Preoperative median neutrophil counts were significantly lower in the DGF group compared to the non-DGF group (4.2 vs. 7.7 [p=0.037]). Furthermore, the median values for PLR and NLR were significantly lower in the DGF group compared to the non-DGF group (145 vs. 219 [p=0.035] and 2.5 vs. 8.2 [p=0.015], respectively). Cut-off values indicated that 11 out of 16 patients who developed DGF had a low preoperative NLR (<5) compared to the non-DGF group (68.8% vs. 34.3%, p=0.023), and 11 out of 16 patients had a low preoperative PLR (<175) compared to the non-DGF group (68.8% vs. 31.4%, p=0.014). In this study, low preoperative PLR and NLR levels were significantly associated with an increased incidence of DGF compared to patients without DGF. The ideal predictive cut-off values for the immuno-inflammatory index were identified as 175 for PLR and 5 for NLR. Low pre-transplant PLR and NLR levels were inversely associated with DGF; therefore, these novel and non-invasive inflammatory biomarkers may contribute to early prediction of DGF in kidney transplant recipients.

Although the included studies addressed the same metric (NLR) in transplant populations, important divergences were observed in the findings. Most adult studies associate elevated NLR with adverse outcomes such as DGF and acute rejection. However, in pediatrics [16], the relationship is reversed, with low NLR values associated with DGF. These discrepancies may reflect physiological variations related to age, distinct inflammatory responses, donor types, and specific immunosuppressive regimens. Studies such as that by Shirakawa et al. [24] also demonstrated a significant reduction in NLR among kidney transplant recipients, suggesting a possible unique immune regulation in this group.

Additionally, distinct methodologies, such as the timing of blood sample collection, diagnostic criteria for DGF, and the absence of adjustments for confounding factors, make direct comparisons between studies challenging. Therefore, it is crucial to consider

these variables when interpreting the results and formulating clinical recommendations based on these metrics. Furthermore, given the frequent cardiovascular risk associated with transplant recipients, investigations like that of Heleniak et al. [25] highlight the importance of a comprehensive risk assessment in the post-transplant period. The application of NLR as an inflammatory marker has also been extended to other areas of transplantology, as demonstrated by Lin et al. [26], who linked elevated NLR levels to poorer outcomes in patients with acute liver failure after liver transplantation.

Overall, there is a trend in adult studies indicating an association between elevated NLR values and worse outcomes, particularly DGF and acute rejection. In contrast, the pediatric study by Siddiqui et al. [16] identified an association between low NLR values and DGF, suggesting possible pathophysiological differences related to age, immune system behavior, immunosuppressive regimen, and systemic inflammatory response. These divergences highlight the importance of stratifying by age and other relevant factors. ROC curve analyses (for example, AUC = 0.664 for NLR in Hogendorf et al. [14]) demonstrate a moderate predictive capacity, insufficient for isolated use as a clinical tool. Additionally, the studies face limitations such as small sample sizes, retrospective bias, and lack of control for variables like infection or corticosteroid use.

While NLR and PLR show potential as prognostic biomarkers, their clinical application still demands caution. Thus, a complementary use integrated with other clinical parameters is proposed. From a practical standpoint, these metrics are attractive due to their simplicity and low cost. However, their incorporation into care protocols requires validation in prospective studies with larger, more robust samples and strict control of confounding variables. It is also essential to define specific cut-off points for different contexts (adults vs. pediatrics, donor type, post-transplant time). The isolated use of NLR, especially with AUCs below 0.7, may lead to inaccurate clinical decisions, making it more appropriate to interpret NLR in conjunction with other markers and clinical variables.

5. Conclusions

This study analyzed the association between the neutrophil-to-lymphocyte ratio (NLR) and outcomes in kidney transplantation. It was found that elevated NLR (>3.5) is associated with delayed graft function (DGF) in adults, whereas low NLR (<5) correlates with DGF in pediatric patients. Despite their promise, hematometric indices still lack sufficient methodological robustness for broad clinical recommendation, due to moderate diagnostic accuracy, sample heterogeneity, and the absence of standardized cut-off points. A complementary use of these indices alongside other clinical and laboratory parameters is suggested. Future studies with prospective designs, larger sample sizes, and stratifications by age and transplant type are essential to consolidate their applicability.

Elevated NLR (>3.5) was associated with DGF in adults, while low NLR (<5) was related to DGF in children. PLR also demonstrated some predictive capacity, though inferior to NLR. Therefore, a complementary use of these indices in pre- and post-transplant evaluation is suggested, based on future, more robust studies. Finally, this work aims to encourage new investigations with larger cohorts and more precise stratifications to validate the effective clinical use of hematologic indices in transplant nephrology.

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