

Hypo-Albuminemia and Perioperative Renal Transplant-Related Infections: A Systematic Review and Meta-Analysis

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Objective: to review the literature regarding the relationship between pre- and post-transplant hypo-Albuminemia with various renal transplant-related infections.

Materials and Methods: In a systematic review, we included the following keywords in the search: (Albumin*) AND (infection*) AND ("renal transplant" OR "renal transplantation" OR "renal transplants") OR ("kidney transplant" OR "kidney transplantation" OR "kidney transplants") OR "kidney grafting") with investigating databases including ProQuest, PubMed, Scopus, and Web of Science to May 2023. All adult patients who had renal transplantation were included. Albumin levels of infected (bacterial, fungal, or viral) patients and the type of infection should be reported in the included studies. The search strategy used in this review was reported by Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension (PRISMA-S). To conduct Meta-analyses, Stata version 17 was used. Also, DerSimonian-Laird random-effects models were used for this study. In our study, heterogeneity was quantified with I² and τ^2 statistics. Inconsistency across studies is quantified by I² statistics, and the impact of heterogeneity on the meta-analysis is assessed by this quantification.

Results: Overall, 18 studies were found to be reporting measures of association including risk ratio, odds ratio, and hazard ratio. Among them, 10 and 8 studies reported bacterial and viral types of infection. The combined risk ratios were not statistically significant, in either type of infection. The mean (SD) of ages for bacterial and viral infections were found to be 45.3 (6.4) and 50.5 (7.6) years old, respectively.

Conclusion: Hypoalbuminemia is not related to post-transplantation infections, and it seems that with adherence to proper pretransplant screening of recipients, vaccination, and post-transplant surveillance and prophylaxis, the impact of infections may be reduced.

Keywords: kidney; transplantation; infection; albumin; rejection

INTRODUCTION

Due to the immunosuppression state that is essential to prevent allograft rejection, opportunistic infections are typical reasons for extensive morbidity and mortality after solid organ transplantation⁽¹⁾. Among kidney transplant recipients, infections are the second most common cause of death⁽²⁾. There are two common infections associated with kidney transplantation: BK polyomavirus (BKV) and cytomegalovirus (CMV)⁽³⁻⁵⁾. Infections with these viruses can cause graft loss and death, making them particularly concerning. There are pieces of evidence that hypoalbuminemia, characteristically defined as serum albumin levels below 3.5g/dl, is related to infectious outcomes in the general population⁽⁶⁻⁸⁾. Chronic systemic inflammation resulting in

diabetic end-stage renal disease (ESRD) may cause hypoalbuminemia due to lower albumin synthesis or increased degradation⁽⁹⁾. Furthermore, inadequate dialysis and malnutrition may also contribute to hypoalbuminemia⁽¹⁰⁾. Several studies have demonstrated that post-transplant hypo-albuminemia is associated with poor one-year graft outcomes, counting CMV infections in kidney and pancreas transplant recipients⁽¹¹⁾. Also, hypoalbuminemia in the pre-transplant population has been associated with reduced post-transplant survival in heart and kidney transplants^(12,13).

To our knowledge, no study investigated infection complications related to kidney transplant recipients (KTRs) based on pre-transplant serum albumin levels. This study aimed to review the literature regarding the

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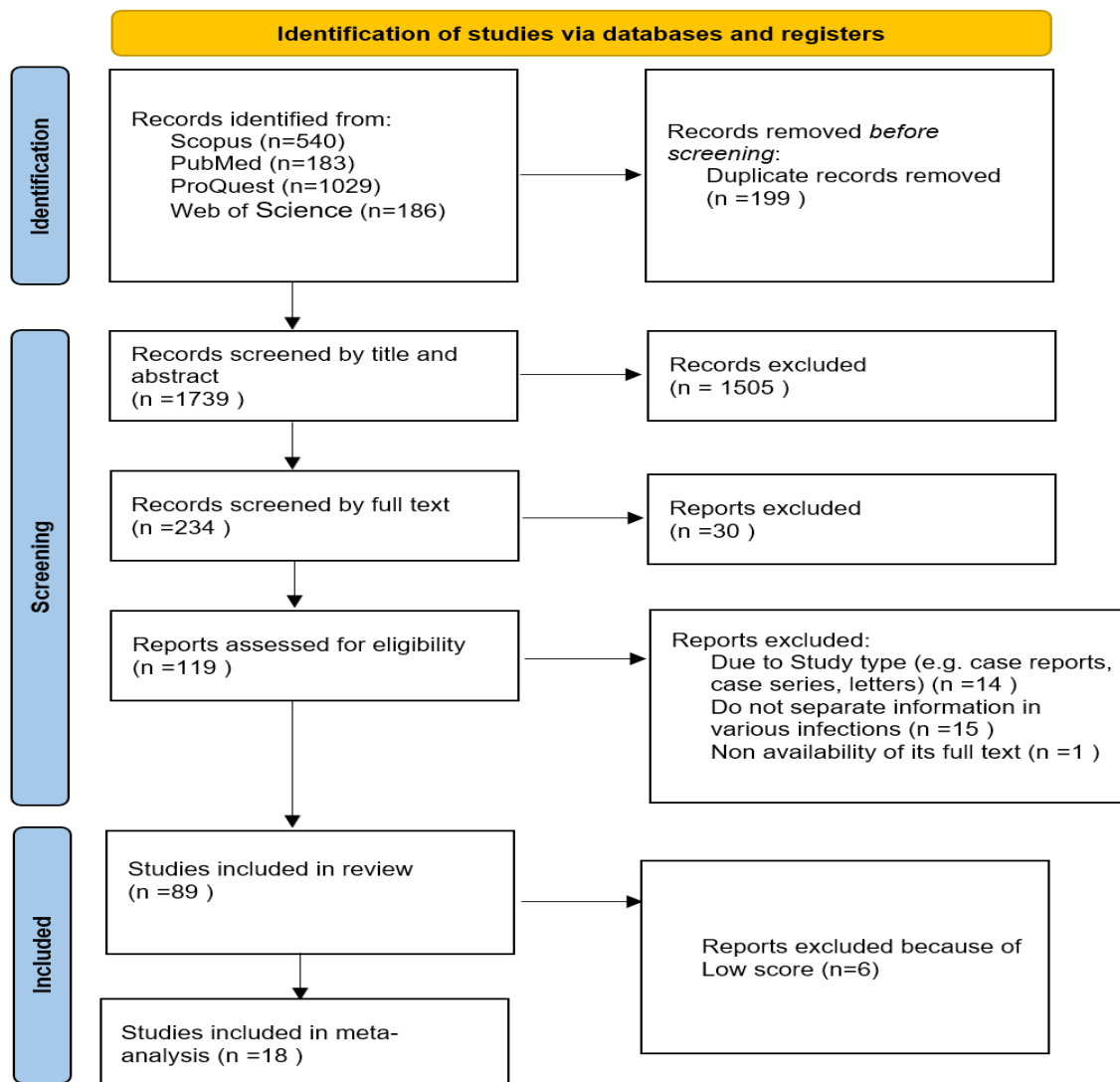


Diagram: Prisma study design and flowchart

relationship between pre- and post-transplant hypoalbuminemia with various renal transplant-related infections.

MATERIALS AND METHODS

The design and methods that are used in the current study were reported by the Centre for Reviews and Dissemination (CRD's) Guidance for Undertaking Reviews in Healthcare⁽¹⁴⁾ and are compiled by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁽¹⁵⁾.

Protocol and registration

The current systematic review was registered under the registration ID CRD42022339945, in the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility Criteria

All observational studies were included, although case reports, case series, letters, correspondence, and commentaries were excluded. All adult patients who had renal transplantation were included. Albumin levels of in-

fect (bacterial, fungal, or viral) patients and the type of infection should be reported in the included studies.

Information sources

In June 2022, ProQuest, PubMed, Scopus, and Web of Science were searched to find eligible studies. After a while, in May 2023, our database was updated; for this purpose, the same methods were used to ensure that all recent and related articles have been included. The other eligible studies or study reports were identified by a 'snowball' search through citation searching (forward and backward citation tracking) using Scopus on all included studies in the current review. Finally, the references of the reviews that were identified with a similar subject to our study were checked to find out whether other potentially eligible studies exist.

Search

The search strategy used in this review was reported by Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension (PRISMA-S)⁽¹⁶⁾. We did not use any restrictions or search filters. Next, a couple of tools were used for recognizing the Free-text terms and keywords, including the MeSH

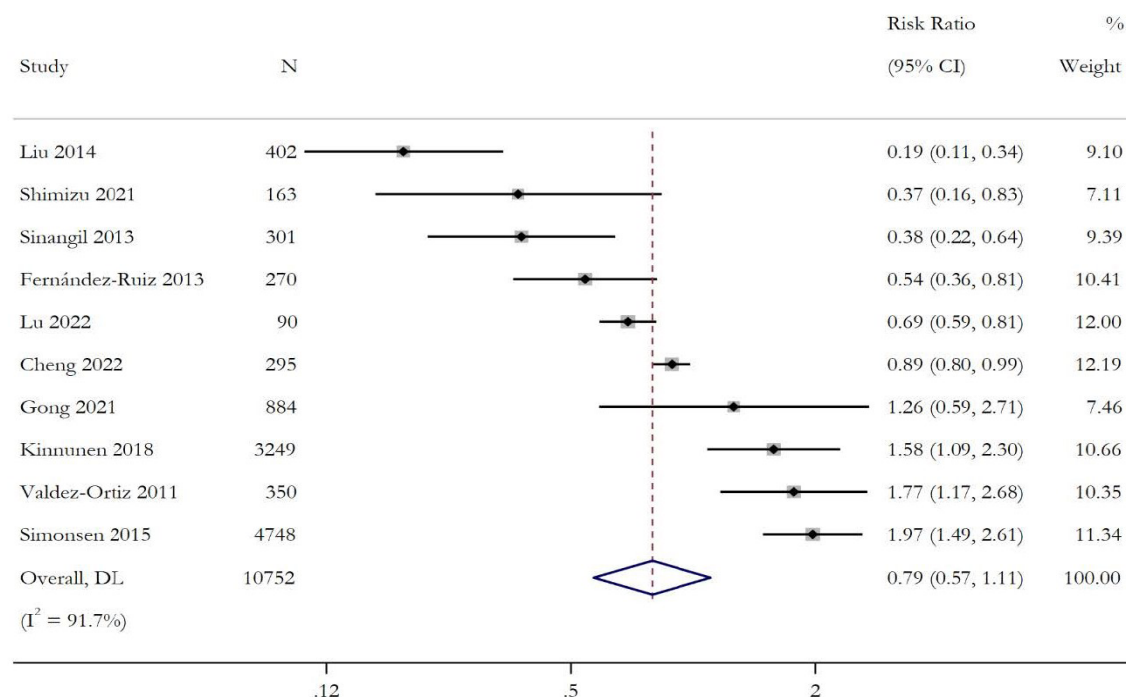


Figure 1. Forest plot of association measures, for bacterial type of infection

Browser⁽¹⁷⁾ website and PubMed PubReMiner⁽¹⁸⁾ word frequency analysis tool. SMKA reviewed the Search strategy according to the Peer Review of Electronic Search Strategies (PRESS)⁽¹⁹⁾ guideline. We included the following keywords in the search: (Albumin*) AND (infection*) AND (("renal transplant" OR "renal transplantation" OR "renal transplants") OR ("kidney transplant" OR "kidney transplantation" OR "kidney transplants") OR "kidney grafting"). Appendix A includes a report of the search strategy in detail.

Study selection

Citations identified from the literature searches and reference list checking were imported to citation manager software called EndNote version 10⁽²⁰⁾. EndNote's deduplication tool was used for finding and excluding duplicates. Then, a web-based application called Rayyan QCRI⁽²¹⁾ was used for importing the remaining records; this tool uses natural language processing, artificial intelligence, and machine learning technologies to speed the screening of titles and abstracts of records. Next, another step of de-duplication was carried out using Rayyan's automatic deduplication feature, with the similarity threshold set to 0.85. After identifying and manually re-checking them, this step removed them. Then, the two reviewers reviewed the titles and abstracts of the first 50 records. Inter-rater reliability was evaluated by Cohen's kappa to be 0.89 (95% CI: 0.85-0.93), which is considered an almost perfect agreement. Next, two reviewers carried out the screening of the titles and abstracts of the retrieved records individually. In case of disagreements, SMKA made the final decision. A full text of any potentially eligible record was retrieved. Then, linking records from the same study was performed to ensure that data from the same study was included just once. Furthermore, the same two reviewers screened full-text studies for inclusion independently. A

study was included when both reviewers independently evaluated it as satisfying the inclusion criteria. SMKA was involved when disagreements existed.

Data collection process

Developing a data extraction form was carried out. In this process, the form was pilot-tested by three reviewers employing five randomly selected studies to evaluate inter-rater reliability. Then, a re-calculation of Inter-rater reliability was performed using Cohen's kappa to be 0.91, which is interpreted as almost perfect agreement. In cases of disagreements, discussions were held until resolved, then the form was used by the same reviewers for extracting data from eligible studies. Comparing the Extracted data was performed and in case of any discrepancies, they were resolved by following discussion. Next, data were imported into Microsoft Excel while double-checking them for possible errors.

Definitions for data extraction

The extracted data includes first author, country, year of acceptance, type of infection, name of infection, study type, total sample size, number of male and female patients, age, BMI, past medical history, smoking, albumin level before and after transplantation, measure of association, number of dead patients, number of graft failure and duration of follow up in years.

Risk of bias

Critical assessment tools for use in JBI Systematic Reviews recommend "JBI's critical appraisal tool". It is considered that this tool is suitable for assessing the bias of included studies^(22, 23). This tool has several sections including patient selection, exposure reliability, confounding factors, and data analysis.

At first, the tool was tested before use. Two reviewers included 20% of studies individually; also, for assessing the inter-rater reliability, Cohen's kappa was 0.75.

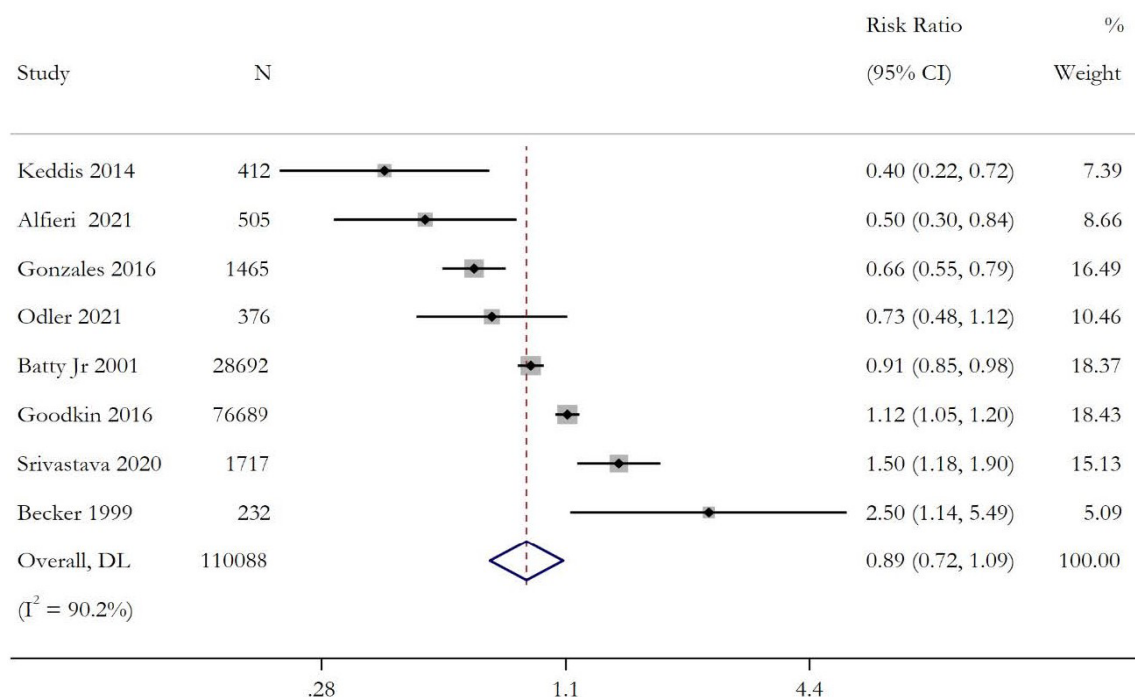


Figure 2. Forest plot of association measures, for viral type of infection

Then, discussions were held to resolve the probable disagreements. Additionally, re-training was carried out. Next, the two reviewers assessed every included study separately. The supporting information and justifications were recorded to measure the risk of bias for every domain (low, unclear, high, or not applicable). SMKA made the final decision in discrepancy situations.

Meta-analysis

To conduct Meta-analyses, Stata version 17 was used⁽²⁴⁾. The included studies had measures of association including risk ratio (RR), hazard ratio (HR), or odds ratio (OR), which their most adjusted versions were merged and reported as risk ratios. Also, DerSimonian-Laird random-effects models were used for this study. In our study, heterogeneity was quantified with I² and τ^2 statistics. Inconsistency across studies is quantified by I² statistics, and the impact of heterogeneity on the meta-analysis⁽²⁵⁾ is assessed by this quantification.

The I² statistic is interpreted as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: represents considerable heterogeneity. The general outcome of our meta-analysis is shown in the forest plots.

Publication bias assessment

Funnel plots were reported to evaluate if the publication bias might have interfered with the mean reliability coefficients obtained in different meta-analyses. This study used the trim and fill method to check the potentially eligible unpublished studies on the plot⁽²⁶⁾. The flowchart of the study is depicted in Diagram 1.

RESULTS

Overall, 18 studies were found to be reporting measures of association including risk ratio, odds ratio, and,

hazard ratio. Among them, 10 and 8 studies reported bacterial and viral types of infection. The findings are presented in **Figures 1 and 2** in the form of forest plots. The combined risk ratios were not statistically significant, in either type of infection. The mean (SD) of ages for bacterial and viral infections were found to be 45.3 (6.4) and 50.5 (7.6) years old, respectively. The result of bias assessment is presented in **Figure 3**.

Moreover, the publication bias assessed through the funnel plots is portrayed in **Figures 4 and 5**. As the graphs indicate, it could be concluded that serious publication bias is present in the data.

DISCUSSION

Renal transplantation is the gold standard treatment in patients with end-stage renal diseases. The life expectancy and quality of life following renal transplantation are nearly equal to those of healthy individuals. Although renal transplantation is superior to chronic dialysis, immunosuppression remains a major concern. Immunosuppressive state related to the increased risk of infections and cancer development. Moreover, there is an increased risk of infection in certain groups such as the elderly or undernourished people with chronic kidney diseases^(2,27).

Infections are the main cause of morbidity and mortality in kidney transplant recipients and rank as the second cause of death in patients. With pretransplant screening of recipients, vaccination, and post-transplant surveillance and prophylaxis, the impact of infections may be reduced. However, because transplant recipients may not manifest typical signs and symptoms of infection due to the immunosuppressive state, diagnoses may be masked⁽²⁾.

Several studies have stated incidences of post-kidney transplantation infections ranging from 15% to 80%.

| Study | Risk of bias | | | | | | | | | | | Overall |
|----------------|--------------|----|----|----|----|----|----|----|----|-----|-----|---------|
| | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | |
| Alfieri | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ? | ⊕ | ⊕ |
| Becker | ⊖ | ⊕ | ⊕ | ⊖ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊖ | ⊕ |
| Cheng | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Fernández-Ruiz | ⊖ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ |
| Gong | ⊖ | ⊕ | ⊕ | ⊖ | ⊖ | ⊕ | ⊕ | ⊕ | ⊖ | ⊖ | ? | ⊕ |
| Kinnunen | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊖ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ |
| Odler | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ? | ⊕ | ⊕ |
| Shimizu | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Valdez-Ortiz | ⊖ | ⊕ | ⊕ | ⊖ | ⊖ | ⊖ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ |
| Lu | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ |
| Simonsen | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Srivastava | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Liu | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Sinangil | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Keddis | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Goodkin | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ |
| Gonzales | ⊕ | ⊖ | ⊕ | ⊖ | ⊕ | ⊕ | ⊕ | ⊕ | ⊕ | ⊖ | ⊕ | ⊕ |

Figure 3: The result of bias assessment.

In developing countries, financial, social, and environmental circumstances may contribute to greater infectious complications⁽²⁸⁻³¹⁾.

The timeline of infections is investigated extensively and is predictable. Within the first month, nosocomial infections are more prevalent, nonetheless in later months (1-6 months) the opportunistic pathogens including cytomegalovirus (CMV), BK polyomavirus (BKV), and Epstein-Barr virus infection (EBV) will be occurred due to the immunosuppressive therapies. The community-acquired will be prevalent after six months.⁽³²⁻³⁴⁾

The main risk factors are investigated in various studies. In a study by Ingsathit et al., they investigated the most common causes of kidney recipient death in 2,298 kidney recipients. The greatest proportion (64%) of deaths was infection owing to septicemia and/or pulmonary infection. The others were from cardiovascular deaths (12%), liver disease (6%), and malignancy (4%)⁽³⁵⁾. This risk of infection increases further in patients in developing or tropical countries. In developing countries, the level of immunosuppression is higher than in developed countries, which could be responsible for the higher incidence of infections.

Among the known risk factors related to infection stated in literature is a decreased level of serum albumin known as hypoalbuminemia. Hypoalbuminemia is a major risk factor for surgical site infection (SSI) in

general surgery. Hypoalbuminemia is associated with the acquisition and severity of infectious diseases, and intact innate and adaptive immune responses depend on albumin⁽³⁶⁻⁴⁰⁾.

In a historical cohort analysis of 33,479 renal transplant recipients in the United States Renal Data System from July 1994 to June 1997, Batty Jr et al. evaluated the prevalence of HCV-positive patients. Among them, 1,624 were HCV positives at the time of transplant (5.7% prevalence). They checked the laboratory data in normal and HCV-positive patients; their results revealed that the normal level of serum albumin was a protective factor for HCV infection (Risk ratio: 0.91, *p*-value < 0.01).

In a study by Keddis et al. on analyses of variables related to 5-year mortality in kidney recipients with diabetes mellitus in 324 patients, they found that serum albumin is significantly related to mortality in this group (risk ratio: 0.397 (0.219-0.720, *p*-value 0.002)⁽⁴¹⁾.

A study by Valdez-Ortiz et al. analyzed 366 transplants in 350 patients, of whom 161 (46%) presented with an episode of infection requiring hospitalization. The incidence rate was 0.46 episodes per 1000 transplant days. Among the risk factors for infection a basal serum albumin concentration < 3.5 mg/dl was significantly related to the infection (RR 1.77, 95% CI 1.17–2.68, *p*-value < 0.001)⁽⁴²⁾.

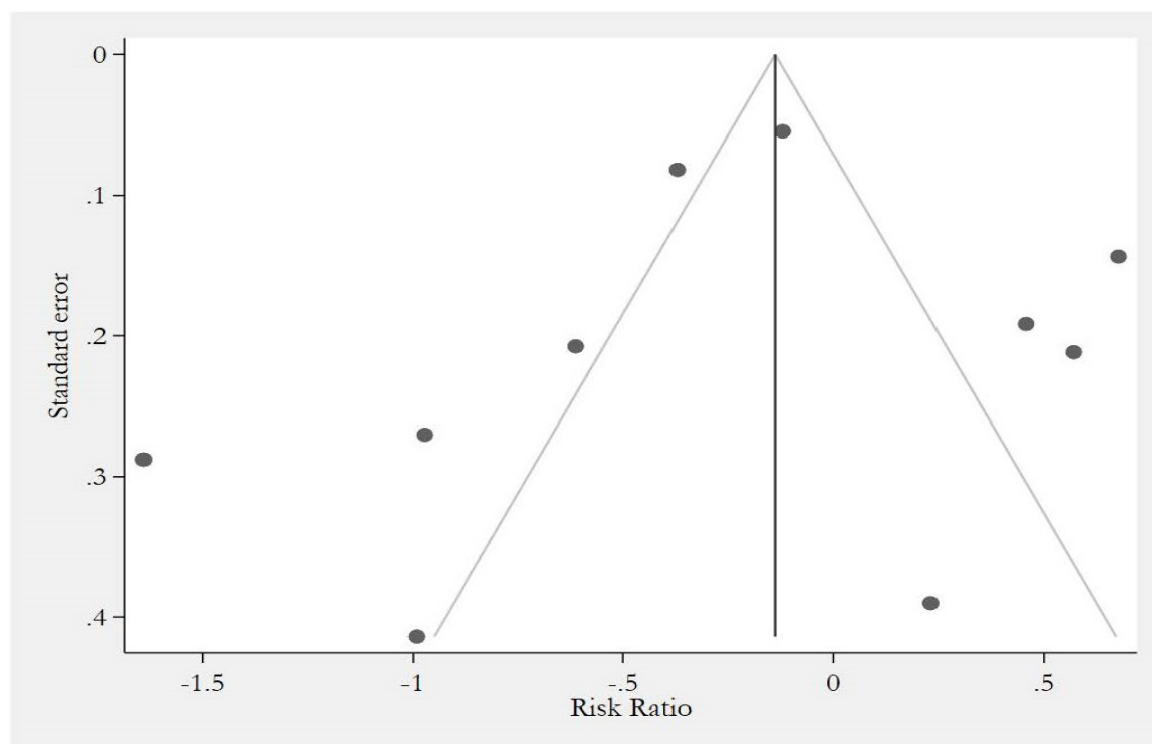


Figure 4. Funnel plot depicting publication bias, for bacterial type of infection

In a cohort study by Wang et al., they evaluated 196 patients undergoing renal transplantation from February 2018 to April 2020. The study included renal transplant recipients who underwent laboratory examinations of BKV-DNA testing in plasma and urine. Their results showed that patients with BK virus active infection were associated with a higher proportion of albumin in serum protein electrophoresis (OR: 1.08, p-value: 0.046)⁽⁴³⁾.

Zieschang et al. investigated risk factors that are associated with mortality in patients after kidney transplants related to non-opportunistic pneumonia. 177 patients (12%) collectively had 270 episodes of pneumonia. Significant risk factors for mortality were C-reactive protein > 10 mg/dL and serum albumin < 3 g/dL on admittance, congestive heart failure, and autosomal dominant polycystic kidney disease as the underlying renal disease. Median serum albumin was 3.30 g/dL (range, 2.53-3.80) in the survivors and 2.50 g/dL (range, 2.15-2.80) in the nonsurvivors (P-value: 0.0031)⁽⁴⁴⁾.

In a study by Guijarro et al., they examined clinical correlates of serum albumin measured at 3 months, 6 months, 1 year, and annually thereafter in 706 renal transplant recipients who survived at least 6 months with a functioning allograft. In multiple linear regression, variables that correlated with lower serum albumin at 3, 6, 12, and 24 months included age, diabetes, proteinuria, and cytomegalovirus infection (P-value < 0.03). They concluded that hypoalbuminemia is a strong independent risk factor for all-cause mortality after renal transplantation (relative risk for each g/dL increment, 0.26, 95% confidence interval, 0.16 to 0.44)⁽⁴⁵⁾.

In a study by Gong et al. they evaluated 866 recipients

who underwent kidney transplant surgery regarding the distribution of pathogens, the resistance rate of MDR bacteria, and the risk factors of MDR bacterial infection. Female gender (OR = 3.497, $P = 0.006$), pathogen types > 1 (OR = 3.832, $P = 0.008$), and postoperative time < 3 months (OR = 0.331, $P = 0.014$) were independent risk factors for MDR bacterial infection. Among the laboratory analysis, the serum albumin was not related to this type of infection (p-value: 0.555, OR: 1.260 (0.586–2.707))⁽⁴⁶⁾.

In a study by Jesús-Gómez et al., on factors that affect complications after renal transplantation, they evaluated 64 patients that underwent renal transplantation in 2002. They also studied postoperative albumin levels and complications. On postoperative day 5, there were 17 patients with albumin below 3 g/dL and 48 patients above 3 g/dL. There was the same incidence of ATN with normal albumin at postoperative day 5, 23% versus albumin below 3 g/dL, 23.5% ($P = .659$). The lymphocyte rate was almost the same, 12.5% versus 11.7% ($P = .653$). They concluded that preoperative albumin of more than 3g/ dl was not a prognostic indicator for the development of surgical complications following renal transplantation. Only preoperative weight, BMI, and dialysis duration were significant factors in the development of postoperative complications and prolonged hospital stay⁽⁴⁷⁾.

In an interesting study by Cheng et al., they evaluated the effects of laboratory parameters on infection after a kidney transplant. This study was a retrospective study, including 295 kidney transplant patients from January 2015 to May 2019. They observed a significant difference in albumin levels between the two groups of infected (n = 85) vs. non-infected (n = 210) patients (p-value:

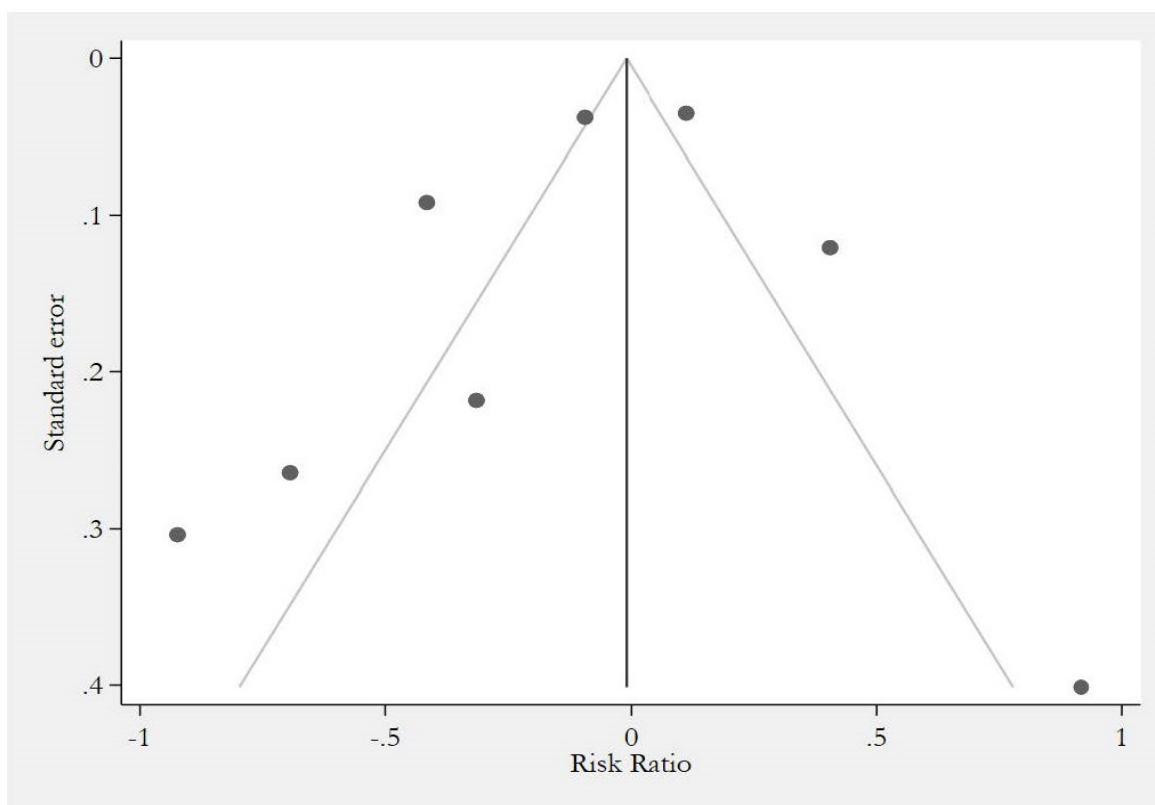


Figure 5. Funnel plot depicting publication bias, for the viral type of infection

0.006). The infected group had lower serum albumin comparing the non-infected patients (30.18 ± 5.96 g/dL vs. 36.22 ± 7.48)⁽⁴⁸⁾.

A cross-sectional study of 402 patients by Liu et al., investigated the correlation between the level of C-reactive protein and serum albumin and the outcome of peritoneal dialysis patients. On multivariate analysis, C-reactive protein level, older age, diabetes mellitus, lower serum albumin level, and the occurrence of cardiovascular events during follow-up were identified as independent predictors of mortality-value: < 0.001 ⁽⁴⁹⁾. In a study by Lu et al., they investigated the risk factors for impaired wound healing after kidney transplantation. A total number of 80 patients (18 with wound infection and 72 patients as control). The factors were analyzed using multivariate Cox regression, showing that BMI > 25 , fasting blood glucose level, albumin level, and prealbumin were the risk factors for impaired wound healing after kidney transplantation (Albumin OR: 0.63 CI: 0.32, 0.86, p-value:0.028)⁽⁵⁰⁾.

In Simonsen et al. study on incidence of bacterial infection in patients with type 1 diabetes, incidence of infection and antibiotics usage were more frequent in patients with macroalbuminuria, and renal transplantation. They used rates ratio (RRs) obtained from the fully adjusted model that was 1.18 (95% CI 1.07 to 1.30) for microalbuminuria, 1.29 (95% CI 1.15 to 1.44) for macroalbuminuria, 2.43 (95% CI 2.08 to 2.84) for dialysis, and 2.74 (95% CI 2.35 to 3.17) for the kidney transplantation group compared to patients with normal albumin excretion rate (AER)⁽⁵¹⁾.

In a single-centre retrospective study on 1,717 kid-

ney transplants by Srivastava et al., they evaluated the recipients' serum albumin within 45 days before transplant and their relationship with viral infection in the postoperative period. Their results revealed that Pre-transplantation hypoalbuminemia is associated with post-transplantation BK virus. Moderate (3.49-2.5 g/dl) and severe hypoalbuminemia (< 2.5 g/dl) increased a higher risk for BKV compared to normal serum albumin levels in univariable analysis (moderate hypoalbuminemia: HR:1.5, 95% CI: 1.14-1.90, $p = 0.003$) severe hypoalbuminemia: HR: 2.15, 95% CI: 1.01-4.56, $p = 0.05$). Although it was not significant after multivariable adjustment, there was still an 18% increased risk in moderate hypoalbuminemia and 64% in severe for BKV compared to the normal albumin group⁽⁵²⁾.

Moderate hypoalbuminemia was associated with a higher risk for CMV infection than normal serum albumin levels in multivariable analysis, although not statistically significant (HR:1.15, 95% CI: 0.36-3.64, $p = 0.81$). These findings suggest that pre-transplantation hypoalbuminemia is associated with a higher risk of post-transplantation BKV and possibly CMV, warranting more intense screening for these viruses in recipients with pre-transplant hypoalbuminemia.

Our systematic review and meta-analysis showed that hypoalbuminemia is not related to post-transplantation infections. The combined risk ratios were not statistically significant, in either type of viral or bacterial infections. The mean (SD) of ages for bacterial and viral infections were found to be 45.3 (6.4) and 50.5 (7.6) years old, respectively.

To sum up, although many studies have stated the rela-

tion of serum albumin level with infections; our results did not show this relationship.

In conclusion, while serious publication bias is present in the available data, hypoalbuminemia is not related to post-transplantation infections, and it seems that with adherence to proper pretransplant screening of recipients, vaccination, and post-transplant surveillance and prophylaxis, the impact of infections may be reduced.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

APPENDIX

<https://journals.sbm.ac.ir/uroj/index.php/uj/libraryFiles/downloadPublic/67>

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