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Impact of Induction Therapy on Preventing Early Acute Kidney Allograft Rejection: A Single-Center Experience Study

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ABSTRACT

Objective: Acute rejection infrequently occurs among immunologically low-risk recipients within the first few weeks after transplantation, and the role of induction treatment in the frequency of acute rejection and graft loss remains debatable.

Materials and Methods: This retrospective study analyzed 208 kidney transplant recipients with low immunological risk, defined by living donor transplantation, no prior transplantation history, absence of preformed anti-HLA antibodies, and a negative lymphocyte crossmatch prior to transplantation. Demographic data, immunologic characteristics, and graft functions were analyzed concerning early acute rejection history.

Results: Fifteen patients (7.2%) experienced acute rejection within two weeks post-transplantation. No correlation was found between the number of HLA mismatches and induction treatment with early acute rejection. The cumulative incidences of acute rejection in the no-induction and basiliximab groups were comparable at 7.8% and 6.4%, respectively. Donor age was markedly higher, and the tacrolimus trough level on the seventh day post-transplantation was significantly lower in the early acute rejection group; however, the significance was lost after adjustment. The incidence of graft loss was higher in the early acute rejection cohort than in the no-rejection cohort (33.3% vs. 3.1%, p<0.001). Early acute rejection was the only independent risk factor for graft failure (HR 10.286, CI 1.944–54.409, p=0.006).

Conclusion: Acute rejection within two weeks post-transplantation has been associated with suboptimal graft function in recipients with low immunological risk. Basiliximab does not provide additional advantages in preventing early acute rejection in patients with a low immunological risk on tacrolimus-based immunosuppression.

Keywords: Acute rejection, basiliximab, immunological risk, immunosuppression, induction, kidney transplantation.

INTRODUCTION

Advancements in immunosuppression have diminished the frequency of acute rejection (AR) and enhanced kidney allograft and patient outcomes in recent decades.[1] Notwithstanding this progress, AR remains a significant contributor to graft loss. In patients with moderate to high immunological risk possessing preexisting donor-specific antibodies (DSA), acute antibody-mediated rejection (ABMR) may occur within the initial weeks after kidney transplantation (KT).[2] Acute T-cell-mediated rejection (TCMR) or de novo DSA-mediated rejection is anticipated in the forthcoming months. While the likelihood of AR is minimal in the initial weeks for unsensitized patients, a few immunologically low-risk individuals may encounter AR shortly after KT.

Induction therapy utilizing an interleukin-2 receptor antagonist (IL-2RA) alongside standard triple maintenance immunosuppression is advised for low-immunological-risk (LIR) kidney transplant recipients (KTRs).[3,4] T-cell-depleting medications are preferred solely for KTRs at high immunologic risk. The risks and advantages of therapy must be weighed, taking into account the side effects associated with immunosuppression. The contribution of induction therapy in low-risk KTRs remains debatable in the context of maintenance involving tacrolimus (TAC), mycophenolate (MPA), and steroids. This study sought to identify risk factors for early acute rejection and the impact of induction therapy in low-immunological-risk patients on standard triple maintenance therapy.

KEY MESSAGES

- Early acute rejection significantly impacts kidney allograft outcomes.
- Basiliximab therapy does not demonstrate a notable effect on the rates of early acute rejection or graft survival in low-immunological-risk kidney transplant recipients receiving tacrolimus-based maintenance immunosuppression.
- A more precise definition of low-immunological risk is essential, along with a revision of recommendations to align with contemporary immunosuppression practices.

MATERIALS AND METHODS

Study Population

A retrospective evaluation was conducted on 349 KTRs who underwent transplantation at our center between January 2010 and January 2019. LIR was characterized as living donor KT, absence of preformed anti-human leukocyte antigen (HLA) antibodies, a negative lymphocyte crossmatch (LCM) prior to transplantation, and no prior transplantation history. The exclusion criteria were established as follows:[1] cadaveric donor KT;[2] pediatric patients under 18 years of age;[3] multiorgan transplantations;[4] two or more prior KTs;[5] patients with a positive LCM;[6] recipients exhibiting anti-HLA antibody positivity;[7] recipients who received induction agents other than IL-2RA; and[8] recipients undergoing maintenance therapy except for TAC, MPA, and steroids.

Two hundred eight LIR recipients were included and classified into groups based on AR occurring within the initial two weeks post-transplantation: (1) the early AR group and (2) the no-early AR group. Data on recipients' age and sex, primary kidney disease, modality and length of kidney replacement therapy, concurrent medical conditions, ABO blood group, number of HLA mismatches, induction and maintenance immunosuppressive medication, as well as donors' age and sex were documented. Serum creatinine (Scr), TAC trough levels (TTL), complications, and graft loss were assessed after KT. The characteristics of patients who received basiliximab and those who were not treated with induction therapy were also assessed.

The Ethical Review Committee of the Ankara University approved the study (Approval ID: İ5-223-19). All protocols complied with the ethical guidelines set forth by the 1975 Helsinki Declaration.

Immunosuppressive Protocol and Posttransplantation Follow-up

A uniform immunosuppressive protocol was implemented for the pretransplant immunological risk evaluation. Recipients of low-risk living-related donors received basiliximab (20 mg on days zero and four) or no induction therapy was administered. The initial maintenance immunosuppression comprised TAC, MPA, and corticosteroids. A pulse of methylprednisolone (500 mg/day for three days) was administered, followed by an ongoing course of 1 mg/kg/day for three days, with a gradual reduction to 4 mg/day in three months. The goal of TTL was 9–10 ng/ml during the initial month, 6–8 ng/ml for the subsequent two months, and 5–8 ng/ml for six months and thereafter. All recipients were administered fluconazole, trimethoprim/sulfamethoxazole, and valganciclovir from the initiation of immunosuppressive medication until three or six months post-KT.

Indication biopsies were conducted due to graft dysfunction or recently developed proteinuria throughout the follow-up period. Rejection events were categorized under the guidance of current Banff criteria into TCMR, ABMR, borderline, or

Table 1. Demographic and immunologic data of kidney transplantation recipients, according to early acute rejection status

	Early AR (+) (n=15, 7.2%)	Early AR (-) (n=193, 92.8%)	p	All patients (n=208, 100.0%)
Recipients' age (years) (Mean±SD)	38.5±11.7	39.5±12.2	0.742	39.5±12.1
Recipients' gender, n (%)			0.524	
Female	7 (46.7)	74 (38.3)		81 (38.9)
Male	8 (53.3)	119, (61.7)		127 (61.1)
ESKD cause, n (%)			0.924	
Glomerulonephritis	4, (26.7)	55 (28.5)		59 (28.4)
Diabetic nephropathy	4, (26.7)	29 (15.1)		33 (15.9)
Hypertensive renal disease	1, (6.7)	21 (10.9)		22 (10.6)
VUR/ PN/ Urolithiasis	1 (6.7)	13 (6.7)		14 (6.7)
Others	2 (13.3)	34 (17.6)		36 (17.3)
Miscellaneous	3 (20.0)	41 (21.2)		44 (21.2)
Kidney replacement therapy, n (%)			0.591	
Hemodialysis	9 (60.0)	100 (51.8)		109 (52.4)
Peritoneal dialysis	0 (0.0)	11 (5,7)		11 (5.3)
Predialysis	6 (40.0)	82 (42.5)		88 (42.3)
Dialysis vintage (months), Median (min–max)	6.5 (2–120)	12 (1–263)	0.877	12 (1–263)
Donors' age (years), Mean±SD	54.3±7.9	47.7±11 .3	**0.040**	48.2±11.2
Donors' gender, n (%)			0.741	
Female	9 (60.0)	124 (64.2)		133 (63.9)
Male	6 (40.0)	69 (35.8)		75 (36.1)
Recipient-donor relationship, n (%)			0.812	
Spouse	4 (26.7)	57 (29.5)		61 (29.3)
Blood relative	10 (66.7)	126 (65.3)		136 (65.4)
Other relatives	1 (6.7)	10 (5.2)		11 (5.3)
HLA Mismatch number, Median (min–max)	3 (1–6)	3 (0–6)	0.679	3 (0–6)
HLA mismatch number ≥3, n (%)	11 (73.3)	122 (63.2)	0.432	133 (63.9)
Induction therapy with basiliximab, n (%)	6 (40.0)	87 (45.1)	0.703	93 (44.7)
TTL at 7th day after KTx (ng/mL) (Mean±SD)	6.7±3.7	8.9±3.5	**0.020**	8.7±3.5

ESKD: End-stage kidney disease; HLA: Human leukocyte antigen; KT: Kidney transplantation; Max: Maximum; Min: Minimum; n: Number; PN: Pyelonephritis; SD: Standard deviation; TTL: Tacrolimus through level; VUR: Vesicoureteral reflux. Bold = p<0.05.

mixed-type rejection. Delayed graft function (DGF), described as acute kidney failure necessitating dialysis within the initial week following KT, was not observed in any of the recipients.

TCMR and borderline rejections were managed with methylprednisolone (500 mg/day for three days) and anti-thymocyte immunoglobulin (ATG, 100 mg/day for three to five days) in instances of steroid unresponsiveness. Active ABMR was managed with a protocol involving methylprednisolone (500 mg/day for three days), plasmapheresis (every other day for up to five sessions or until Scr levels reached 20–30% of baseline), and intravenous immunoglobulin (100 mg/kg following each plasmapheresis session). Only one patient was administered rituximab (once, 375 mg/m^2) due to rapidly deteriorating graft function, which did not adequately respond to initial ABMR treatment.

Statistical Analysis

Continuous data were reported as mean (standard deviation) for normally distributed numerical variables or median

Table 2. Graft outcomes of kidney transplantation recipients, according to early acute rejection status

	Early AR (+) (n=15, 7.2%)	Early AR (-) (n=193, 92.8%)	p
sCr at 1st month after KTx (mg/dl), Median (min–max) (n=164)	1.68 (0.90–4.13)	1.18 (0.41–2.04)	**0.010**
sCr at 3rd month after KTx (mg/dl), Median (min–max) (n=103)	1.57 (0.90–3.75)	1.15 (0.65–2.04)	**0.014**
sCr at 6st month after KTx (mg/dl), Median (min–max) (n=153)	1.55 (0.87–2.52)	1.14 (0.45–3.05)	<**0.001**
sCr at 12th month after KTx (mg/dl), Median (min–max) n=145	1.34 (0.92–3.33)	1.11 (0.59–2.14)	**0.023**
Recurrent AR, n (%)	5 (33.0)	0 (0.0)	<**0.001**
BK virus infection, n (%)	6 (42.9)	40 (20.7)	0.105
Graft loss, n (%)	5 (33.3)	6 (3.1)	<**0.001**
Follow-up (months), Mean±SD	38.5±11.7	47.5±30.3	0.884

AR: Acute rejection; KT: Kidney transplantation; Max: Maximum; Min: Minimum; n: Number; sCr: Serum creatinine; SD: Standard deviation. Bold = p<0.05.

(minimum–maximum) for non-normally distributed numerical variables, whereas nonparametric data were given as n (%). The Student's t-test was employed for normally distributed numerical data, while the Mann-Whitney U test was utilized for non-normally distributed numerical variables. The difference between categorical variables was analyzed using the Chi-square or Fisher exact test. Factors associated with early AR were analyzed using logistic regression. Variables with a p-value<0.10 from univariate analyses were incorporated as possible factors in the regression model. The final model was determined via the forward stepwise elimination (Forward LR) approach, with odds ratios (OR), 95% confidence intervals (CI), and Wald statistics computed for each variable. Kidney allograft survival among early AR groups was assessed using Kaplan-Meier survival analysis, complemented by the Log-Rank test. A multiple Cox regression analysis was conducted to calculate hazard ratios (HR) for independent risk factors.

The statistical analysis was conducted using IBM Statistical Package for Social Sciences version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA). A p-value<0.05 was deemed statistically significant.

RESULTS

Baseline Characteristics

The mean age of KTRs was 39.5±12.1 years, with 61.1% being male (Table 1). The predominant etiologies of primary kidney disease included glomerulonephritis, diabetic kidney disease, and hypertensive nephropathy, with 21.1% of cases having an unidentified primary kidney disease. A total of 57.7% of KTRs were undergoing dialysis, while the remainder had preemptive transplants. The median dialysis vintage was 12 months, with a range of 1 to 263 months. The donors had a mean age of 48.2±11.2 years at KT, with 63.9% being female. The majority of donors were blood-related (65.4%), with 40.4% classified as first-degree relatives, and 29.3% were spouses.

A total of 133 patients (63.9%) had HLA mismatches ranging from 3 to 6. Ninety-three (44.7%) KTRs underwent induction treatment with basiliximab. In comparison to recipients in the no-induction cohort (n=115, 55.3%), individuals receiving basiliximab were predominantly non-blood relatives (84.7% vs. 22.8%, p<0.001), older (44.1 vs. 35.7 years, p<0.001), and exhibited a greater frequency of HLA mismatches (≥3MM 60.9% vs. <3MM 16.0%, p<0.001).

Comparison of Acute Rejection

Within the two-week period following KT, 15 patients (7.2%) had an AR episode, which was predominantly identified within the first week post-transplantation (7.2±3.6 days). Rejection incidents were categorized as TCMR (n=5, 33.3%), ABMR (n=2, 13.3%), borderline (n=5, 33.3%), and mixed-type rejection (n=3, 20.0%). The primary indicator suggesting AR was elevated Scr levels [2.38 mg/dl (1.34–9.21)], which improved with AR treatment [1.70 mg/dl (0.81–4.13)].

No demographic differences were noted between the early AR and no-early AR groups, with the exception of donor age (54.3±7.9 vs. 47.7±11, p=0.040) (Table 1). The HLA mismatch number was not correlated with early AR (p=0.679). The frequency of AR development was comparable in recipients who did not receive induction therapy and those who received basiliximab therapy (7.8% vs. 6.4%, p=0.703). TTLs within the first week post-KT were considerably reduced in the early AR group (6.7±3.7 vs. 8.9±3.5, p=0.020, respectively).

In multivariate analysis, increased donor age and elevated TTL had no significant correlation with early AR (OR 1.045, p=0.100 and OR 0.853, p=0.066, respectively); nonetheless, a protective trend was noted regarding higher TTL.

Table 3. Factors affecting graft survival

Graft loss	Univariate analysis		Multiple analysis	
	HR (%95 CI)	p	HR (%95 CI)	p
Recipient age	0.986 (0.939–1.037)	0.590		
Recipient gender (female → male)	4.004 (1.062–15.099)	**0.041**	3.339 (0.766–15.548)	0.108
Kidney replacement treatment (dialysis → preemptive)	5.739 (0.732–44.987)	0.096	5.646 (0.719–44.341)	0.100
Donor age	0.966 (0.908–1.028)	0.271		
HLA mismatches (≥3 → <3)	1.379 (0.366–5.199)	0.635		
Basiliximab treatment (yes → no)	0.430 (0.126–1.470)	0.178	1. 822 (0.470–7.067)	0.386
TTL at 7th day after transplantation	0.914 (0.763–1.095)	0.331		
AR at first two weeks (yes → no)	9.711 (2.954–31.926)	<**0.001**	10.286 (1.944–54.409)	**0.006**
Recurrent AR (yes → no)	11.500 (3.013–43.895)	<**0.001**	0.592 (0.719–44.341)	0.623

AR: Acute rejection; CI: Confidence interval; HLA: Human leukocyte antigen; HR: Hazard ratio; TTL: Tacrolimus through level. Bold = p<0.05.

Comparison of Graft Outcomes

Patients were followed for approximately 4 years (47.6±30.3 months). During follow-up, Scr levels were markedly increased in the early AR group compared to the no-early AR group (Table 2). Early posttransplant AR was an important risk factor for the recurrence of AR (p<0.001). In the early AR group, five patients (33.3%) had graft loss, whereas six patients (3.1%) in the no-early AR group encountered graft failure (p<0.001). The frequency of graft loss did not differ substantially regarding induction therapy (3.5% in the no-induction cohort versus 7.5% in the basiliximab cohort, p=0.225).

The reasons for graft loss included chronic graft failure (4 patients, 36.4%), recurrent glomerulonephritis (2 patients, 18.2%), infection or sepsis (2 patients, 18.2%), and acute rejection (3 patients, 27.2%).

Female recipient sex, early AR, and recurrent AR correlated with diminished graft survival; however, early AR was independently associated with graft loss (HR 10.286, CI 1.944–54.409, p=0.006) (Table 3, Fig. 1).

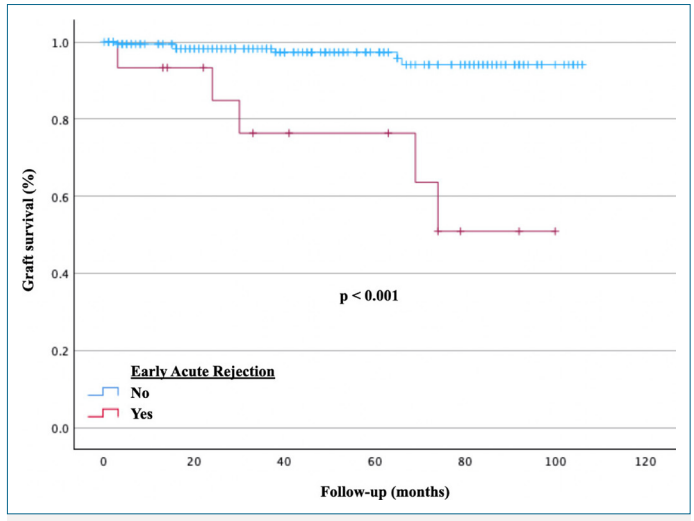

Figure 1. Kaplan-Meier plot showing cumulative allograft survival by early acute rejection status.

DISCUSSION

In this retrospective analysis, we outlined the clinical characteristics, treatment modalities, and graft functions of our LIR patients based on early AR status, which may assist in the management of immunosuppressive medication for these individuals. We established that early AR was a prevalent consequence that resulted in diminished graft function, even in LIR recipients. Basiliximab treatment does not significantly influence the frequency of early AR or graft survival in low-risk recipients using TAC/MPA-based maintenance immunosuppression; nevertheless, TTL is a crucial predictor of rejection risk.

A greater number of HLA mismatches, a younger recipient age, an older donor, anti-HLA antibody positivity, the presence of DSA, blood incompatibilities, delayed graft function, and prolonged cold ischemia time are recognized risk factors for AR.[3] In our low-immunological-risk KTRs, we did not observe any significant relation between early AR and the number of HLA mismatches or recipient age; however, patients with zero HLA mismatches exhibited a tendency to have no AR compared to KTRs with 1 to 6 HLA mismatches.

Early clinical studies indicate that IL-2RA decreased AR within the first year post-KT, accompanied by fewer adverse events. However, studies involving living donor KTRs on TAC/MPA/

steroid maintenance immunosuppression suggest that it may not substantially affect outcomes like rejection rates or graft survival. Despite the 2009 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline advocating for the use of induction therapy with IL-2RA in KTRs at low immunological risk, no randomized, controlled, double-blind clinical studies have been conducted under modern maintenance immunosuppression.

A retrospective analysis of data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/STR) revealed that IL-2RA induction therapy significantly influenced AR when combined with TAC/MPA; however, the absolute benefit was inferior to that of cyclosporin-based regimens.[9] Tanriover et al.[10] demonstrated that, in a cohort of 36,153 living donor KTRs with HLA mismatches ranging from 1 to 6, IL-2RA induction did not yield superior results compared to no-induction therapy when TAC/MPA/steroids were administered. This extensive retrospective research excluded KTRs with zero HLA mismatch. In deceased donor KTRs on standard triple therapy, particularly those classified as low-risk, the reduction in AR risk associated with any induction therapy was minimal.[11]

Low-risk recipients, identified as first-time transplants with anti-HLA antibodies<20% and HLA mismatch<3, who underwent transplantation from the same donor with TAC/MPA immunosuppression, exhibited comparable AR and graft survival rates between those who received IL-2RA or ATG and those who did not.[12] However, patient survival rates were better in individuals who received induction therapy. An additional study implementing the OPTN registry indicated that the administration of induction therapy did not correlate with enhanced graft and patient outcomes among first adult kidney KTRs who were optimally matched with their donors.[13]

Data from the Collaborative Transplant Study involving 38,311 first deceased donor KTRs from 2004 to 2013 were categorized as "normal risk" or "increased risk" in accordance with current KDIGO recommendations.[14] This data indicates that ATG and IL-2RA induction therapy did not positively impact the reduction of AR during the first year of normal-risk transplantations. The analysis of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) on KTRs from 1995 to 2005 indicated no decline in rejection risk associated with IL-2RA, regardless of whether recipients were classified as low or intermediate immunological risk if they were under TAC-based maintenance.[15] Recently, Lacave et al.[16] reported the outcomes of KTRs from deceased donors and retransplantations in anti-HLA antibody-free recipients prior to transplantation, revealing no advantage of basiliximab on the rates of AR and graft survival over a 5-year period.

Our investigation, along with the aforementioned studies, demonstrated that basiliximab provided no supplementary advantage regarding the frequency of AR during the initial two weeks post-transplantation. The preference for basiliximab among older persons, non-blood relatives, and transplants with a greater number of HLA mismatches may have contributed to this outcome. Despite excluding patients with pretransplant DSA, a risk factor for AMR-related graft loss,[17] we did not monitor de novo DSA in our KTR cohort. Nonetheless, de novo DSA has been demonstrated to be significantly associated with AMR and reduced allograft survival.[18]

Consequently, we conclude that LIR must be properly outlined, and immunosuppressive therapy should be customized to balance the benefits against potential adverse effects, including infection and cancer in these patients. In accordance with current guideline recommendations, the majority of KTRs globally continue to receive induction therapy. Given the existing evidence, it is essential to define LIR more precisely and revise guidelines regarding induction treatment in LIR patients under triple immunosuppressive therapy comprising TAC, MPA, and steroids.

Administering TAC to KTRs in substitution for cyclosporin led to a decrease in AR and an enhancement in graft survival.[19] Regarding the higher likelihood of AR in recipients with lower TTL during the initial post-transplant phase, it is recommended to sustain a 12-hour TTL in the range of 10–15 ng/mL for the first two months following KT and then reduce the dosage.[20–23] Our prior research has established that maintaining TTLs at least 8 ng/mL during the initial month effectively avoids biopsy-confirmed AR with minimal toxicity.[24] Both low TTLs and significant intrapatient variability were risk factors for unfavorable transplant outcomes.[25–27]

Our study demonstrated that achieving the TTL target earlier was correlated with a reduced incidence of AR events, irrespective of induction treatment. Consistent with our findings, De Sandes-Freitas et al.[28] observed no distinction in the frequency of AR in low-risk KTRs with the incorporation of IL-2RA into a tacrolimus-based immunosuppressive protocol, and the TTLs were comparable in patients with or without induction.

The primary strength of our study is the uniformity of maintenance immunosuppressive treatment. However, our research possesses some limitations. The limited sample size

and retrospective design of the study may permit residual confounding. The statistical analysis and interpretation of the data are constrained by the small patient sample and should not be extrapolated to the entire population of transplant patients. To derive more accurate findings, additional prospective research with substantial sample sizes is required.

We established LIR based on donor type, transplant count, anti-HLA antibody presence, and LCM results. We noted that additional criteria, including HLA matching and the occurrence of de novo DSA, also characterize immunological risk. The fact that de novo anti-HLA antibodies, DSA, and non-HLA antibodies were not monitored in our study may have led to limitations in immunological risk assessment. The absence of agreement on the definition of LIR utilized in clinical trials complicates data interpretation.

This study was performed on low-risk KTRs, and no extrapolation of these results is permissible. The length of follow-up was insufficient to determine the long-term effect of induction on graft outcomes.

CONCLUSION

In summary, basiliximab does not confer further advantages in preventing early AR, a critical predictor of graft loss, nor does it enhance outcomes in low-risk KTRs undergoing TAC/MPA-based immunosuppressive therapy. A higher target for TTL should be established in these individuals to prevent early AR, irrespective of induction treatment. Future extensive prospective studies are required to more precisely specify the necessity, type, and dosage of immunosuppression in low-risk KTRs.

Ethics Committee Approval: The Ankara University Human Research Committee granted approval for this study (date: 14.11.2019, number: İ5-223-19).

Author Contributions: Concept –GK, KK; Design – GK, KK; Supervision – AFK, AT, SS, KK; Resource – GK, SE, DOS, AFK, AT, SS, KK; Materials – GK, KK, SE, DOS; Data Collection and/or Processing – GK, KK, SE, DOS; Analysis and/or Interpretation – GK, KK; Literature Search – GK, KK; Writing – GK; Critical Reviews – GK, SE, DOS, AFK, AT, SS, KK.

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