Review article

Therapeutic efficacy of extracellular vesicles to suppress allograft rejection in preclinical kidney transplantation models: A systematic review and meta-analysis

Yitian. Fang, Sarah Bouari, Martin J. Hoogduijn, Jan N.M. Ijzermans, Ron W.F. de Bruin, Robert C. Minnee

A Erasmus MC Transplant Institute, Division of HPB and Transplant Surgery, Department of Surgery, Erasmus MC University Medical Center, Rotterdam, the Netherlands
B Erasmus MC Transplant Institute, Nephrology and Transplantation, Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Background: Kidney transplantation is the optimal treatment of end-stage renal disease. Extracellular vesicles (EVs) have tremendous therapeutic potential, but their role in modulating immune responses in kidney transplantation remains unclear.

Methods: We performed a systematic review and meta-analysis to investigate the therapeutic efficacy of EVs in preclinical kidney transplantation models. Outcomes for meta-analysis were graft survival and renal function. Subgroup analysis was conducted between immune cell derived EVs (immune cell-EVs) and mesenchymal stromal cell derived EVs (MSC-EVs).

Results: Seven studies published from 2013 to 2021 were included. The overall effects showed that EVs had a positive role in prolonging allograft survival (standardized mean difference (SMD) = 2.00; 95% confidence interval (CI), 0.79 to 3.21; P < 0.01; I² = 94%), reducing serum creatinine (SCr) (SMD = -2.19; 95%CI, -3.35 to -1.04; P < 0.01; I² = 93%) and blood urea nitrogen (BUN) concentrations (SMD = -1.69; 95%CI, -2.98 to -0.40; P = 0.01; I² = 94%). Subgroup analyses indicated that only immune cell-EVs significantly prolonged graft survival and improve renal function but not MSC-EVs.

Conclusions: EVs are promising candidates to suppress allograft rejection and improve kidney transplant outcome. Immune cell-EVs showed their superiority over MSC-EVs in prolonging graft survival and improving renal function. For interpretation of the outcomes, additional studies are needed to validate these findings.

1. Introduction

Extracellular vesicles (EVs) are membranous particles that can be released by a variety of cells. Referring to minimal information for studies of extracellular vesicles 2018 (MISEV2018), EVs can be broadly divided into small EVs (sEVs, <100 or 200 nm) and medium/large EVs (m/MEVs, >200 nm) [1]. Initially, these structures were regarded as waste products. However, there is now a consensus that EVs carry a cargo of proteins, nucleic acids, lipids, etc. and play an important role in intercellular communication by releasing their vesicular cargoes after being taken up by target cells [2-5].

Kidney transplantation is the optimal treatment of end-stage renal diseases. However, lifelong use of immunosuppressants increases the risk of opportunistic infections, malignancies, cardiovascular diseases and diabetes mellitus [6-9]. One major aim in transplantation research is to reduce or eliminate the use of immunosuppressive agents [10]. Recently, research on EVs showed their potential in immune modulation and therapeutic applications [11,12]. In terms of transplantation,
studies have focused on their roles in alleviating immune rejection, improving graft function and enhancing graft survival [13]. To the best of our knowledge, there has been no study that has systematically investigated the possible effects of EVs on alleviating graft rejection, and thus enhancing graft survival. Therefore, we conducted this systematic review and meta-analysis to evaluate the therapeutic efficacy of EVs in preclinical kidney transplant models.

2. Materials and methods

This review adheres to the preferred reporting items for systematic reviews and meta-analyses statement [14].

2.1. Search strategy

A literature search was performed in the Embase, Medline, Web of Science, and Cochrane Central databases. Searches were conducted using MeSH and EMTREE keywords. Detailed search strategies are included in Table S1. The final literature search was performed on February 10th, 2022.

2.2. Eligibility criteria

Studies were eligible based on the following inclusion criteria: (1) population—allogeneic kidney transplant model; (2) intervention—EV-based treatment; (3) comparison—untreated or placebo; and (4) outcome—allograft survival and/or postoperative renal function. Exclusion criteria for studies were as follows: (1) non-English studies; (2) insufficient information; (3) specific types of studies (e.g., reviews, letters, case reports, conference abstracts, editorials, and replies).

2.3. Data extraction

Data extraction was performed by two independent reviewers (YF and RWFdB) based on the eligibility and exclusion criteria. Disagreements between YF and RWFdB were solved by consensus or a third reviewer (RCM). The following study parameters were collected: first author, publication year, species of the donor and recipient, type of EVs, number of animals, cellular origins and dose of EVs, administration methods, therapy and measurement time, allograft survival and postoperative renal function. For studies that did not show specific raw data, WebPlot Digitizer version 4.5 was used to extract data from the graphics.

2.4. Quality assessment

YF and RWFdB independently assessed the evidence quality of each included study using the systematic review centre for laboratory animal experimentation (SYRCLE) risk of bias tool [15]. SYRCLE’s risk of bias tool is based on the Cochrane Collaboration Risk of Bias Tool and adapted to animal studies, which contains 10 entries. These entries are related to 6 forms of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. A “yes” judgment indicates low risk of bias, a “no” judgment indicates high risk of bias, an “unclear” judgment indicates that insufficient data could be retrieved from the study to properly assess the risk of bias.

2.5. Statistical analysis

All statistical analyses were conducted using RevMan version 5.4 and StataSE. Continuous outcomes are expressed as the standard mean difference (SMD) with the 95% confidence intervals (CIs). Heterogeneity
Table 1: Characteristics of included studies.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Donors</th>
<th>Group size</th>
<th>EV size</th>
<th>EV origin</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Measurement</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiello et al. [18] 2017</td>
<td>Male BN rats</td>
<td>Control, n = 4</td>
<td>50-100 nm</td>
<td>Syngeneic Treg</td>
<td>EVs from 100 × 10^6 Tregs</td>
<td>Intravenous Day −1</td>
<td>Day 7, 14, 30, 60</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Aiello et al. [18] 2017</td>
<td>Male LEW rats</td>
<td>Control, n = 4</td>
<td>50-100 nm</td>
<td>Syngeneic Treg</td>
<td>EVs from 25 × 10^6 Tregs</td>
<td>Intraspinal Day 0</td>
<td>Day 7, 14, 30, 60</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Koch et al. [19] 2015</td>
<td>Male LEW rats</td>
<td>Control, n = 6</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Day 1</td>
<td>Day 5, 7</td>
<td>Renal function</td>
<td>Immune response</td>
<td></td>
</tr>
<tr>
<td>Pang et al. [20] 2019</td>
<td>Male C57BL/6 mice</td>
<td>Control, n = 10</td>
<td>&lt; 220 nm</td>
<td>Syngeneic imDC</td>
<td>10 μg</td>
<td>Intravenous Day −1, 1</td>
<td>Day 6</td>
<td>Graft survival</td>
<td>Immune response</td>
<td></td>
</tr>
<tr>
<td>Pang et al. [20] 2019</td>
<td>Female BALB/c mice</td>
<td>Control, n = 10</td>
<td>&lt; 220 nm</td>
<td>Syngeneic mDC</td>
<td>10 μg</td>
<td>Intravenous Day −1, 1</td>
<td>Day 6</td>
<td>Graft survival</td>
<td>Immune response</td>
<td></td>
</tr>
<tr>
<td>Ramirez-Bajo et al. [21] 2020</td>
<td>Male Fischer rats</td>
<td>Control, n = 42</td>
<td>160-500 nm</td>
<td>Allogeneic ADMSC</td>
<td>1 × 10^8 EVs</td>
<td>Intravenous Day 0</td>
<td>Week 1, 4, 8, 12</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Ramirez-Bajo et al. [21] 2020</td>
<td>Male LEW rats</td>
<td>Control, n = 42</td>
<td>160-500 nm</td>
<td>Allogeneic BMSC</td>
<td>1 × 10^8 EVs</td>
<td>Intravenous Day 0</td>
<td>Week 1, 4, 8, 12</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Ramirez-Bajo et al. [21] 2020</td>
<td>Male Fischer rats</td>
<td>Control, n = 42</td>
<td>160-500 nm</td>
<td>Allogeneic BMSC</td>
<td>1.4 × 10^8 EVs</td>
<td>Intravenous Week 0, 4, 8</td>
<td>Week 1, 4, 8, 12</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Ramirez-Bajo et al. [21] 2020</td>
<td>Male LEW rats</td>
<td>Control, n = 42</td>
<td>160-500 nm</td>
<td>Syngeneic ADMSC</td>
<td>1.4 × 10^8 EVs</td>
<td>Intravenous Week 0, 4, 8</td>
<td>Week 1, 4, 8, 12</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Wang et al. [22] 2021</td>
<td>Male SD rats</td>
<td>Control, n = 14</td>
<td>&lt; 200 nm</td>
<td>Allogeneic BMSC</td>
<td>1.4 × 10^8 EVs</td>
<td>Intravenous Day −1, 1</td>
<td>Day 7</td>
<td>Immune response</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Wu et al. [23] 2022</td>
<td>C57BL/6 mice</td>
<td>Control, n = 14</td>
<td>100 nm</td>
<td>Allogeneic BMSC</td>
<td>10 μg</td>
<td>Intravenous Day −1, 1</td>
<td>Day 6</td>
<td>Immune response</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Yu et al. [24] 2013</td>
<td>Male BN rats</td>
<td>Control, n = 15</td>
<td>30-100 nm</td>
<td>Allogeneic Treg</td>
<td>11.7 μg</td>
<td>Intravenous Day 1, 3, 5</td>
<td>Day 1, 3, 5, 7, 14, 21</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Yu et al. [24] 2013</td>
<td>Male LEW rats</td>
<td>Control, n = 15</td>
<td>30-100 nm</td>
<td>Allogeneic B cell</td>
<td>9.6 μg</td>
<td>Intravenous Day 1, 3, 5</td>
<td>Day 1, 3, 5, 7, 14, 21</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Yu et al. [24] 2013</td>
<td>Male BN rats</td>
<td>Control, n = 15</td>
<td>30-100 nm</td>
<td>Syngeneic Treg</td>
<td>11.7 μg</td>
<td>Intravenous Day 1, 3, 5</td>
<td>Day 1, 3, 5, 7, 14, 21</td>
<td>Graft survival</td>
<td>Renal function</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADMSC, adipose-derived mesenchymal stromal cell; BMSC, bone marrow mesenchymal stromal cell; BN, Brown-Norway; EV, extracellular vesicle; imDC, immature dendritic cell; mDC, mature dendritic cell; SD, Sprague-Dawley; Treg, regulatory T cell.

a,b The day of transplantation was considered as Day 0.

was evaluated by I^2 statistic. If there was significant heterogeneity (I^2 statistic >50%) [16], subgroup analysis was performed in a random effects model. Statistical significance was set at p-value <0.05 (two-tailed). Because of the limited studies, the publication bias was not assessed [17].

3. Results

3.1. Search results

The database searches yielded 161 studies. After screening of titles and abstracts, 16 studies remained for full-text assessment of eligibility.

Finally, 9 studies were excluded due to unqualified animal models and interventions, 7 were included in this systematic review and meta-analysis [18–24]. The overview of the study selection process is outlined in Fig. 1.

3.2. Study characteristics

The general characteristics for each eligible study are presented in Table 1. All studies were published between 2013 and 2021, with a total of 248 animals in 7 control groups (n = 98) and 14 experimental groups (n = 150). The experimental animals are either rats (n = 204) or mice (n = 44). The strains include Lewis (RT1^a, LEW), Lewis.1 U (LEW.1 U,
RT1<sup>u</sup>, Brown Norway (RT1<sup>u</sup>, BN), Fischer-344, Wistar and Sprague-Dawley (SD) rats, or C57BL/6 and BALB/c mice. Fig. 2 illustrates the sources of EVs applied in these studies. Seven groups used mesenchymal stromal cells (MSCs), including bone marrow mesenchymal stromal cell (BMSCs, <i>n</i> = 5) and adipose-derived mesenchymal stromal cells (ADMSCs, <i>n</i> = 2), and 7 used immune cells, including regulatory T cells (Tregs, <i>n</i> = 4), dendritic cells (DCs, <i>n</i> = 2), and B cells (<i>n</i> = 1). Eight groups used EVs from syngeneic origin and 6 used allogeneic ones. Most

Fig. 2. Origins for extracellular vesicle (EV) extraction and characterization. ADMSC, adipose-derived mesenchymal stromal cell; BMSC, bone marrow mesenchymal stromal cell; imDC, immature dendritic cell; mDC, mature dendritic cell; Treg, regulatory T cell.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>Year</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu 2013</td>
<td>21</td>
<td>2.17</td>
<td>15</td>
<td>6.8</td>
<td>0.94</td>
<td>15</td>
<td>7.4%</td>
<td>8.26 [5.91, 10.62]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Yu 2013</td>
<td>14.1</td>
<td>2.47</td>
<td>15</td>
<td>6.8</td>
<td>0.94</td>
<td>15</td>
<td>9.2%</td>
<td>3.80 [2.55, 5.06]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Yu 2013</td>
<td>18.8</td>
<td>2.54</td>
<td>15</td>
<td>6.8</td>
<td>0.94</td>
<td>15</td>
<td>8.3%</td>
<td>6.10 [4.29, 7.90]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Aiello 2017</td>
<td>15</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>8.2%</td>
<td>1.44 [-0.44, 3.32]</td>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>Aiello 2017</td>
<td>23.3</td>
<td>3.31</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>8.0%</td>
<td>1.71 [-0.31, 3.73]</td>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>Pang 2019</td>
<td>12.5</td>
<td>5.21</td>
<td>10</td>
<td>10.9</td>
<td>4.7</td>
<td>10</td>
<td>9.7%</td>
<td>0.31 [-0.57, 1.19]</td>
<td>2019</td>
<td></td>
</tr>
<tr>
<td>Pang 2019</td>
<td>15.6</td>
<td>4.4</td>
<td>10</td>
<td>10.9</td>
<td>4.7</td>
<td>10</td>
<td>9.6%</td>
<td>0.99 [0.05, 1.93]</td>
<td>2019</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>71</td>
<td></td>
<td>73</td>
<td>60.5%</td>
<td></td>
<td></td>
<td></td>
<td>3.11 [1.25, 4.96]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: <i>Tau^2</i> = 5.56; <i>Chi^2</i> = 73.85, df = 6 (<i>P</i> < 0.00001); <i>I^2</i> = 92%
Test for overall effect: <i>Z</i> = 3.29 (<i>P</i> = 0.001)

Fig. 3. Forest plot showing the efficacy of immune cell and MSC derived extracellular vesicles (EVs) in prolonging graft survival.

RT1<sup>u</sup>, Brown Norway (RT1<sup>u</sup>, BN), Fischer-344, Wistar and Sprague-Dawley (SD) rats, or C57BL/6 and BALB/c mice. Fig. 2 illustrates the sources of EVs applied in these studies. Seven groups used mesenchymal stromal cells (MSCs), including bone marrow mesenchymal stromal cells (BMSCs, <i>n</i> = 5) and adipose-derived mesenchymal stromal cells (ADMSCs, <i>n</i> = 2), and 7 used immune cells, including regulatory T cells (Tregs, <i>n</i> = 4), dendritic cells (DCs, <i>n</i> = 2), and B cells (<i>n</i> = 1). Eight groups used EVs from syngeneic origin and 6 used allogeneic ones. Most
studies injected EVs intravenously within the time range of one day before to one day after kidney transplantation. Four studies reported the allograft survival and the other three did not because they sacrificed all animals on day 6 and 7 after transplantation. Postoperative serum creatinine (SCr) concentrations were reported in all studies. Blood urea nitrogen (BUN) concentrations were reported in three studies.

3.3. Graft survival

Graft survival was analyzed in four studies [18,20,21,24], using 195 animals. The overall effect showed that EVs could significantly prolong allograft survival (SMD = 2.0; 95%CI, 1.25 to 4.96; \( P < 0.01; I^2 = 92\%\), while no significance was found between the MSC derived EVs (MSC-EVs) and control groups (SMD = 0.36; 95%CI, -1.05 to 1.78; \( P = 0.61; I^2 = 94\%\). The graft survival increased by 1.6 to 14.2 days in the immune cell-EVs group and by 6.8 to 19.8 days in the MSC-EVs group. A subgroup analysis was then conducted in the immune cell-EVs group between syngeneic and allogeneic EVs (Fig. 4). The result indicated that both subgroups can significantly prolong graft survival (Syngeneic: SMD = 2.01; 95%CI, 0.29 to 3.74; \( P = 0.02; I^2 = 88\%\); allogeneic: SMD = 5.92; 95%CI, 1.55 to 10.28; \( P < 0.01; I^2 = 91\%\)).

3.4. Postoperative renal function

Postoperative SCr concentrations were analyzed in seven studies [18–24], using 233 animals. The overall effect showed that SCr concentrations were significantly lower in the experimental groups (SMD = 3.1; 95%CI, 0.29 to 3.74; \( P = 0.02; I^2 = 88\%\); allogeneic: SMD = 5.92; 95%CI, 1.55 to 10.28; \( P < 0.01; I^2 = 91\%\)).
2.19; 95% CI, -3.35 to -1.04; P < 0.01; I² = 93%; Fig. 5). Immune cell-EVs significantly reduced postoperative SCR concentrations (SMD = -4.93; 95% CI, -8.66 to -1.20; P = 0.01; I² = 95%), whereas MSC-EVs did not (SMD = -0.77; 95% CI, -1.79 to 0.26; P = 0.14; I² = 91%). The SCR concentrations decreased by -1.19 to 28.87 mg/dL in the immune cell-EVs group and by -0.55 to 1.89 mg/dL in the MSC-EVs group. Postoperative BUN concentrations were analyzed in three studies [21,22,24], using 168 animals. The overall effect showed that BUN concentrations were significantly lower in the experimental groups (SMD = -1.69; 95% CI, -2.98 to -0.40; P = 0.01; I² = 94%; Fig. 6), but the effect was also limited to the immune cell-EVs group (SMD = -4.83; 95% CI, -5.89 to -3.77; P < 0.01; I² = 0%) rather than the MSC-EVs group (SMD = -0.58; 95% CI, -1.69 to 0.52; P = 0.30; I² = 92%). The BUN concentrations decreased by 25.91 to 30.95 mg/dL in the immune cell-EVs group and by 41.13 to 20.1 mg/dL in the MSC-EVs group. Due to the limited number of studies, further subgroup analysis was not conducted.

3.5. Quality Assessment

All included studies were assessed with the SYRCLE’s risk of bias tool. There was a high risk of selection bias in 5 studies as they did not report whether animals were randomly allocated to treatment and control groups [18–21,23]. One study was judged “high risk” in the section of attrition bias because some animals were excluded from the experiment on day 1 after transplantation without explaining if the missing data were likely to affect the actual outcome [19]. The details of the quality assessment are shown in Fig. 7.

4. Discussion

As far as we know, this is the first systematic review and meta-analysis of the EV therapy in kidney transplantation. Our results show that EVs have the potential to prolong graft survival and improve renal function. In the presence of allogeneic rejection, the therapeutic efficacy of immune cell-EVs is prominent, but the role of MSC-EVs becomes insignificant.

Recently, many studies have been published focusing on the value of EVs in renal diseases. In clinical trials, EVs were reported as a potential biomarker of renal function [25,26], antibody-mediated rejection [27,28], and kidney fibrosis [29]. In preclinical trials, it has been previously shown that MSC-EVs can ameliorate renal ischemia-reperfusion injury (IRI) [30,31]. However, research on the efficacy of EVs to prevent graft rejection is quite limited. Through our literature search, eight studies were found evaluating the therapeutic effect of EVs in renal transplant models. One study was excluded since a syngeneic transplant model was used [33]. The remaining 7 studies all used MHC-mismatched transplant models, which mimicked the graft rejection in the clinic.

Compared to the immune cell-EVs, MSC-EVs had no beneficial effect, either on renal function or graft survival. Indeed, MSC-EVs possess the capability to inhibit apoptosis and stimulate proliferation in tubular epithelial cells in IRI models [11,30–32]. They were also documented to regulate immune responses by suppressing the proliferation of T cells, B cells and DCs in vitro [34–36]. However, these effects become insignificant with allograft models in vivo due to the ongoing process of rejection. A subgroup analysis was conducted in the immune cell-EVs group, which showed that both syngeneic and allogeneic immune cell-EVs were significantly effective in prolonging graft survival. Contrary to our finding, Hoffmann et al. reported that Tregs from naïve donor mice can rescue recipients from lethal graft-versus-host disease after allogeneic transplantation, but this protective effect occurred only when the Tregs were of donor but not recipient origin [37]. The mechanism behind this difference is relevant to HLA typing of EVs but remains still unclear. Considering the relevant literature is quite limited, more studies are urgently needed to confirm whether there are differences between syngeneic and allogeneic EVs in suppressing graft rejection.

To confirm if EVs were beneficial on graft survival due to the immune modulation, histopathological and immunological changes were analyzed in all studies. The allogeneic Treg derived EVs were proved to suppress T cell proliferation and postpone graft rejection [18,24]. Pang et al. showed that the inflammatory response and the number of CD4+ T cells was reduced with the intervention of syngeneic imDC-EVs [20]. The study by Ramirez-Bajo et al. revealed that allogeneic ADMSC-EVs reduced T, B, and NK cell infiltration in the graft but allogeneic BMSC-EVs had little effect [21]. Contrarily, the other two studies indicated that with allogeneic BMSC-EVs, the reduction of inflammatory response and CD4+ T cell infiltration was found in H&E and CD4 antibody staining sections [22,23]. In addition, Koch et al. observed that the number of T cells and B cells was even higher with the administration of syngeneic BMSC-EVs [19].

Another interesting finding is that besides the studies we have included, Aiello et al. also evaluated the efficacy of combining Treg-EVs together with immunosuppressants [18]. Surprisingly, when recipient rats received Treg-EVs with supplementation of low-dose cyclosporine (CsA, 5 mg/kg) within the first four days after transplantation, acute
rejection was avoided and graft survival was further prolonged, with 75% of recipient rats achieving long-term survival and displaying stable SCr concentrations. Since long-term graft survival cannot be achieved solely by EVs, the combination of EVs and low dose immunosuppressants would be a promising strategy to ensure graft survival and reduce the immunosuppressive load.

Our meta-analysis has several limitations that need to be addressed. Firstly, the heterogeneity between studies was high (I², 92% to 94%) for our primary analyses. Subgroup analyses were performed to minimize the heterogeneity, but it was not significantly reduced, which may...
weaken the stability of the results. Secondly, there is heterogeneity in rat or mouse strains between studies. LEW-BN, Fischer-LEW, LEW.1 U-LEW, SD-Wistar and C57BL/6-BALB/c strain combinations are fully MHC-mismatched whereas the Fischer-LEW strain combination differs in a minor histocompatibility locus, and is regarded as a model of chronic, rather than acute allograft rejection [38–41]. Since the number of MHC mismatches is an important risk factor for allograft loss in renal transplantation [42], fully MHC-mismatched models of different strain combinations share a similar role in the graft outcome. Thirdly, since there is still no general rule to specifically characterize each EV subtype, we classified the EVs into immune cell-EVs and MSC-EVs according to the cellular origin, which is recommended by MISEV2018.

In conclusion, EV therapy is a promising approach to suppress allograft rejection and improve transplant outcomes in the field of kidney transplantation. In terms of the cellular origin, immune cell-EVs and MSC-EVs were superior over MSC-EVs in prolonging graft survival and meanwhile reducing the immunosuppressive load. These findings enrich the literature and provide directions for cell-free therapy in the future. However, before applying it to a clinical setting, more in vivo studies are needed to elucidate the optimal cellular origin, dosage, and treatment schedule.

Authorship
Y.F.: Participated in research design, methodology, data collection, formal analysis, statistical analysis, figures and manuscript preparation.
S.B.: Participated in data collection and writing manuscript.
M.J.H.: Participated in writing manuscript.
J.N.M.I.: Participated in writing manuscript.
R.W.F.D.: Participated in research design, data collection, and writing manuscript.
R.C.M.: Participated in research design and writing manuscript.

Declaration of Competing Interest
The authors declare no conflicts of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.trr.2022.100714.

References


