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Review Article

Allotransplanting donor kidneys after resection of a small renal cancer or contralateral healthy kidneys from cadaveric donors with unilateral renal cancer: a systematic review

Yu N, Fu S, Fu Z, Meng J, Xu Z, Wang B, Zhang A. Allotransplanting donor kidneys after resection of a small renal cancer or contralateral healthy kidneys from cadaveric donors with unilateral renal cancer: a systematic review.

Abstract: This systematic review summarizes evidence on allotransplantation of donor kidneys after resection of a small renal cancer or contralateral healthy kidneys from cadaveric donors with unilateral renal cancer. Eligible studies were identified by screening four bibliographic databases, contacting key authors, and analyzing the bibliographies of included studies. Two reviewers independently assessed the reports for inclusion and extracted data, which were summarized as a narrative review. In the 20 case report or case series studies included in the analysis, there were 97 documented cases of donor kidney transplantation after resection of small renal cancer without pathologically confirmed recurrence, whereas 22 cases used contralateral healthy kidneys from cadaveric donors with unilateral renal cancer with one case of cancer recurrence. These results suggest that the use of donor kidneys after resection of small renal cancer is associated with a relatively low cancer recurrence rate.

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Although cancer is generally not considered a transmissible disease, direct transmission from one host to another has been documented in rare circumstances. One such example is the immunosuppressive condition following organ transplantation with the donor organ harboring an occult

malignancy. Donor-transmitted cancers emerged in a relatively large number of cases in the pioneering era of transplantation, before the risk of transmission was recognized (1). The transplant community has since learned that the presence of most cancers, including renal cancer, is a contraindication to organ donation (2).

For patients with end-stage renal failure (ESRF), renal transplantation confers a more significant improvement in quality of life and survival advantage than those of patients on dialysis. However, in the current era of donor organ scarcity, a significant number of ESRF patients, especially those who have severe medical problems during dialysis, die from the complications of chronic renal insufficiency on long-term dialysis before they are able to receive a transplant (3). Various measures including the use of marginal donors have been adopted to increase the donor pool. As small renal cancer (SRC; <4 cm) is associated with a low malignant potential, some transplant institutions have used donor kidneys with SRC despite the contraindications regarding the presence of malignancy. Contralateral healthy kidneys from cadaveric donors with unilateral renal cancer are also been used for transplantation. Several recent studies have analyzed the effect of the use of such donor kidneys on cancer transmission. However, a systematic review on this topic is not available. In this study, we performed a systematic review of the literature and summarized the current evidence on the use of such controversial donor sources.

Methods

Literature search

An initial search of the PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov databases was conducted without language constraints to collect all relevant data. The search strategy and keywords used were as follows: in PubMed, (carcinoma, renal cell [MeSH Terms]) AND Kidney Transplantation (MeSH Terms) or donor kidney renal cancer; in EMBASE, intensive search with the words kidney cancer and renal graft, and limited search with human, kidney carcinoma; in Cochrane Library, using the Title Abstract keywords kidney, transplantation, renal cancer (word variations have been searched); In ClinicalTrials.gov, kidney, transplantation, and renal cancer. A manual search was also performed in the ClinicalTrials.gov database to avoid publication bias. We further refined the search by examining the bibliographies of the included studies.

Inclusion and exclusion criteria

Studies had to satisfy the following two criteria for inclusion in the analysis: (i) kidneys with SRC (<4 cm) were transplanted and (ii) extensive cancer resection had been conducted (tumor-free margin confirmed by pathology) before the transplantation. Studies describing allotransplantation of contralateral healthy kidneys from donors with unilateral renal cancer were also included.

The criteria for exclusion were as follows: (i) studies without follow-up or detailed information; (ii) kidneys from donors who were on chemotherapy or radiation therapy for renal cancer prior to the nephrectomy; and (iii) donors or recipients who had concurrent non-renal malignancies.

Selection of studies

Studies were selected according to the following process: two reviewers screened the titles and abstracts of all articles retrieved. Duplicated reports were removed. Potentially eligible studies were identified based on the inclusion and exclusion criteria. All articles deemed potentially eligible were retrieved in full text. Full-text articles were screened independently by two reviewers using a predesigned and piloted eligibility assessment form. Disagreements on eligibility decisions were resolved by consensus or by recourse to a third party in the review team.

Data extraction and management

In cases of duplicate publications of a particular study, the most recent and most complete data were used in the analysis. Incomplete data from a given case were supplemented with data from subsequent publications in the absence of published integrated data.

Data from all included studies were extracted independently by two reviewers using pre-designed and piloted forms. Extracted data included study type, first author and publication year, number of total cases, number of selected cases, tumor diameter, pathology, follow-up, graft function, cancer recurrence, and recipient survival. Corresponding authors of relevant studies were contacted to obtain information if necessary. Any disagreements were resolved by consensus or by recourse to a third party in the review team.

Data synthesis

Data were combined as a narrative review with supporting tables. Cancer recurrence rates from individual studies were summarized.

Results

Nature of studies included

As shown in Fig. 1, 1680 articles were identified using the search strategy described above, and 1604 were excluded after removing duplicates and scanning the titles and abstracts. Of the remaining 76 articles, 48 did not meet our inclusion criteria after the full texts were examined thoroughly. Of the 28 articles that met our inclusion criteria, 11 showed duplication of information from five studies and another two articles were excluded at this stage because required information could not be obtained. Finally, 20 studies were selected for this systematic review. Studies with high-level evidence, such as randomized controlled trials, were not found on this topic. The 20 studies included were all case series or case reports.

Allotransplantation of kidneys with incidentally found SRC during kidney recovery or live donor evaluation after tumor resection

The incidental detection of SRC during renal recovery occurs in 0.9% of all donor kidneys (4). However, most of these kidneys may not have been allotransplanted, reported, or recognized; the transplantation of such kidneys after resection of renal cancer has only been reported in a small number of cases. The first such report was published by Stubenbord et al. (5), who described the detection of a 3-cm calcified avascular lesion in the donor kidney

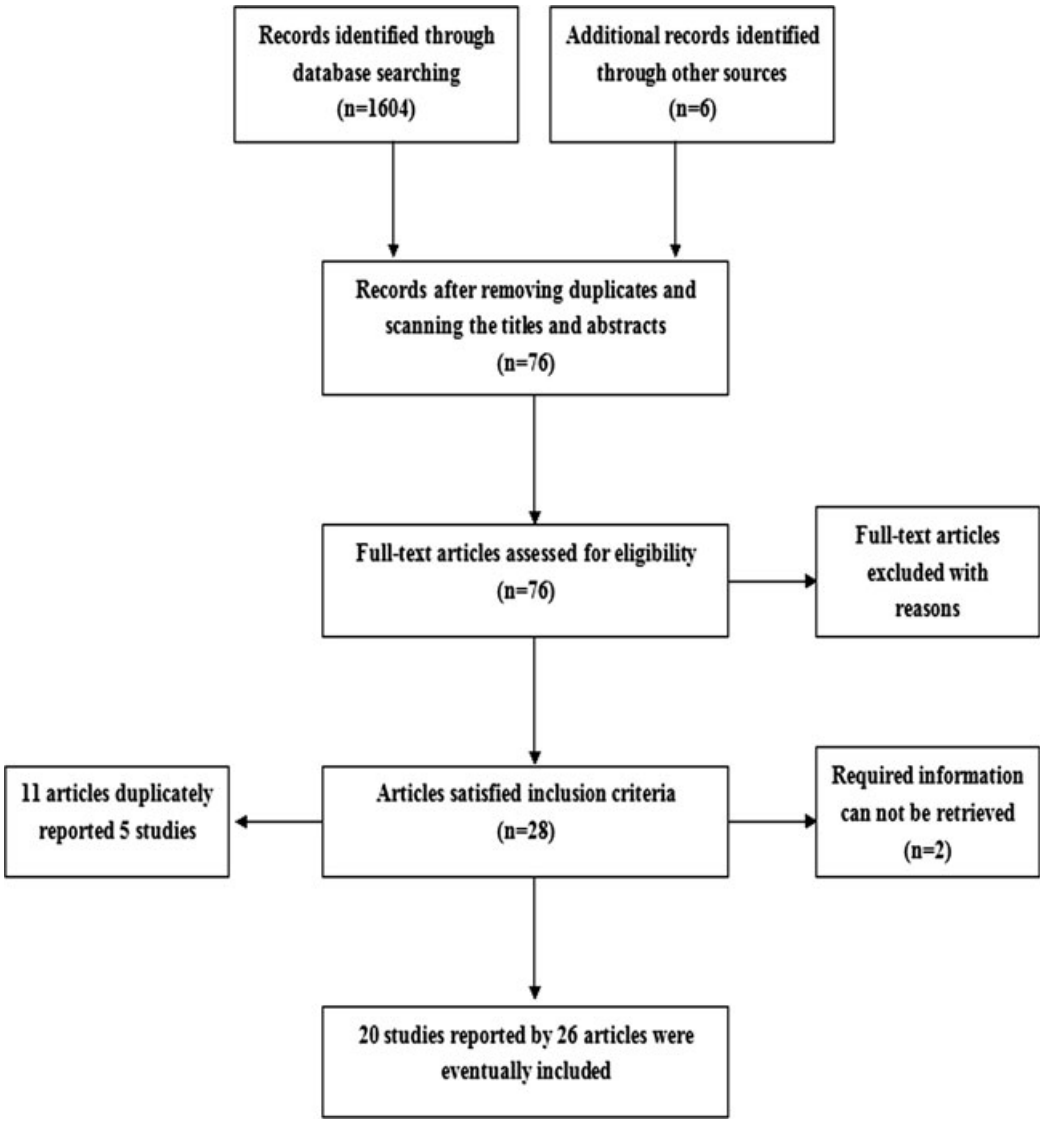

Fig. 1. PRISMA flowchart depicting inclusion and exclusion decisions: records were identified from PubMed (n = 932), EMBASE (n = 641), and Cochrane Library (n = 31). Two trials were identified from Clinicaltrials.gov. A manual search by scrutinizing the bibliographies of included studies identified six more records.

during live donor evaluation without a feasible fast pathologic diagnosis. The kidney was transplanted after extensive resection of the malignant lesion, which was confirmed by pathologists as ossified renal cell carcinoma at 24 h after the transplantation (5). It showed an excellent allograft function without cancer recurrence for up to eight yr of follow-up. The largest case series report was that of Buell et al. in 2005, which summarized 14 such cases from the largest and most comprehensive transplant tumor registry in the world, the Israel Penn International Transplant Tumor Registry (8 of the 14 cases had been reported by Penn (6)). In that study, no recurrence was observed for up to a follow-up period of 200 months. Median tumor size was 2.0 cm (range 0.5–4.0 cm), and all tumors were of low histologic grade (7). Similar cases were reported by Weiss et al. (8), Lasaponara et al. (9), Dainys et al. (10), and Ghafari et al. (11), one case each; three cases were reported by Sener et al. (12); one case was reported by Bycroft et al. (13); one case was reported by Hijosa et al. (14); two cases were reported by Ali et al. (15); and one case was reported by Valente et al. (16). There was no cancer recurrence in any of these 11 cases for up to a follow-up period of 138 months. Detailed information is shown in Table 1.

Allotransplantation of kidneys from patients previously diagnosed with SRC

As shown in Table 2, several clinical trials have investigated the allotransplantation of kidneys from patients previously diagnosed with SRC. In 2007, Whitson et al. reported the transplantation of a kidney from a 22-yr-old man who underwent laparoscopic radical nephrectomy for a 2-cm central renal mass to a 62-yr-old man with ESRF after resection of the tumor. The recipient had excellent graft function without cancer recurrence or metastasis during a follow-up period of two yr (17). In 2008, Nicol et al. reported the results of 31 renal transplantations performed by using kidneys with SRC after tumor resection. In that series, one possible recurrence was reported in a mean follow-up of 32 months, which consisted of a small lesion remote from the initial site of resection that was detected nine yr post-transplantation. In this case, the patient refused treatment, and during a two-yr observation period, the lesion grew from 1 to 1.2 cm. However, the nature of the lesion was never determined (18). In this series of patients, the outcomes were similar to those of conventional live unrelated transplants, and the treatment conferred a significant survival advantage in patients who would otherwise be unable to receive a transplant (19). In 2008, Mannami et al. reported the results of allotransplantation using eight donor kidneys with SRC without any case of recurrence (20). Ogawa et al. performed two prospective clinical trials (ClinicalTrials.gov NCT 00980317 and NCT-00994188) to study living renal transplantation with restored kidneys, and their latest report in 2012 describes the use of 10 donor kidneys with SRC without any recurrence (21). In February 2007, the Western Australia Kidney Transplant

Table 1. Transplantation of kidneys with incidentally found small renal cancer during kidney recovery or live donor evaluation after tumor resection

First author, yr	Country	Total case number	Included case number	Tumor diameter (cm)	Pathology	Up to follow-up	Graft function	Cancer recurrence	Recipient survival
Valente M, 2012 (16)	Italy	3	1	0.8	Grade I RCCC	52 M	–	None	Yes
Ali AM, 2012 (15)	UK	2	2	0.5 1.4	RCCC	4 Y 6 Y	Good	None	Yes
Hijosa MM, 2012 (14)	Spain	1	1	2.5	Grade I RCCC	8 Y	Good	None	Yes
Bycroft JA,[a] 2010 (13)	UK	1	1	0.7	pRCC	–	Good	None	Yes
Sener A, 2009 (12)	USA	5	3	<2.3	1 Grade III pRCC 1 Grade II RCCC 1 Grade II cRCC	31 M	Good	None	1 Dead 2 Alive
Ghafari A, 2007 (11)	Iran	1	1	0.5	Grade I pRCC	15 M	Good	None	Yes
Dainys B, 2007 (10)	Lithuania	1	1	2	RCCC	6 Y	Good	None	Yes
Buell JF, 2005 (7)	US	14	14	0.5–4	8 Grade II 6 Grade I RCC	200 M	–	None	–
Lasaponara F, 2000 (9)	Italy	1	1	1	Grade II RCC	138 M	Good	None	Yes
Weiss SG, 1998 (8)	USA	1	1	1	RCC	10 Y	–	None	Yes
Stubenbord WT, 1982 (5)	USA	1	1	3	oRCC	8 Y	Good	None	Yes

RCC, renal cell carcinoma without subtype pathology information; RCCC, renal clear cell carcinoma; pRCC, papillary renal cell carcinoma; cRCC, cystic renal cell carcinoma; oRCC, ossified renal cell carcinoma; –, information cannot be retrieved.
[a]A fully excised pRCC rather than a tumor-free margin was determined by pathology.

Table 2. Allotransplantation of kidneys from patients previously diagnosed with small renal cancer

First author, yr	Country	Total case number	Included case number	Tumor diameter (cm)	Pathology	Up to follow-up	Graft function	Cancer recurrence	Recipient survival
He B, 2012 (22)	Australia	24	20	1.7–3.3	17 RCCC 2 pRCC 1 chRCC	55 M	–	None	–
Ogawa Y, 2012 (21)	Japan	10	10	<4	RCC	27 M	–	None	Yes
Brook NR, 2010 (19)	Australia	43	31	1–2.9	25 RCCC 5 pRCC 1 chRCC	32 M	–	One possible recurrence	–
Mannami M, 2008 (20)	Japan	42	8	1.5–3.5	RCC	135 M	2 Dysfunction	None	5 Alive
Whitson JM, 2007 (17)	United States	1	1	2	Low-grade chRCC	2 Y	Good	None	Yes

RCC, renal cell carcinoma without subtype pathology information; RCCC, renal clear cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; –, information cannot be retrieved.

Service set up a program to restore kidney grafts from urologist referrals for renal transplant, and the latest results were reported in 2012. The corresponding author, who was contacted recently, reported that a total of 20 donor kidneys with SRC had been used for transplantation, and no recurrence had been observed (22).

Our systematic literature review showed that including incidental and planned cases, to date, 97 documented transplantations using donor kidneys with SRC after tumor resection were performed, and no pathologically confirmed recurrence was reported.

Allotransplantation of contralateral kidneys from cadaveric donors with unilateral renal cancer

Deceased donor transplantation using the remaining contralateral "healthy" kidney from patients with unilateral renal cancer is not recommended by most transplant surgeons because of concerns related to micrometastasis and the bilaterality of certain renal cell carcinomas. However, several studies have reported the use of such kidneys for transplantation. In 1988, Pliskin et al. (23) described the use of cadaver donor kidneys with no cancer recurrence. Penn summarized 14 such cases from the Israel Penn International Transplant Tumor Registry, among which de novo cancer of the native kidney was reported in one patient and verified to originate from the recipient. The remaining patients did not have any cancer recurrence within a follow-up period ranging from 0.5 to 153 months (6). Other similar cases were reported as follows: one case from Carver et al. (24), two cases from Brook et al. (19), and one case from Valente et al. (16). No cancer recurrence was detected in any of these five cases up to a follow-up of 56 months. Barrou et al. reported a case of transplantation of the left kidney from a donor with a 17-mm tubulopapillary tumor in the right kidney. A biopsy performed three months after transplantation because of rejection revealed a poorly differentiated cancer. The recipient underwent radical allograft nephrectomy; treatment consisted of discontinuation of immunosuppressants, and no additional chemotherapy was administered. Lymph node enlargement detected by CT scan disappeared two months after nephrectomy. The patient underwent retransplantation two yr later and was cancer-free and dialysis-independent at the three-yr follow-up (25).

Overall, 21 cases of contralateral healthy kidney transplantation from cadaveric donors with unilateral renal cancer have been reported with only one case of cancer recurrence (cancer recurrence rate: 4.8%). Detailed information is shown in Table 3.

Overview of non-included relevant literature

Takahara et al. (26) reported on the transplantation of five kidneys with SRC after removal of the malignant lesion in Uwajima City Hospital; however, no ethical discussion or detailed records were included, and the study was excluded because of lack of information. The transplantation of two kidneys from donors with renal cancer in the Centre-Sud Transplant Organization in the south of Italy was described by Fiaschetti; however, this study was excluded because detailed information could not be obtained from the article and the authors did not reply to our inquiries (27).

Several studies reported the detection of allograft renal cancer after transplantation (28). In

Table 3. Allotransplantation of contralateral kidneys from cadaveric donors with unilateral renal cancer

First author, yr	Country	Case number	Tumor diameter (cm)	Pathology	Follow-up	Cancer recurrence
Valente M, 2012 (16)	Italy	2	1.5 0.2	Grade II RCCC	56 M 22 M	None
Brook NR, 2010 (19)	Australia	2	–	RCCC	32 M	None
Barrou B, 2001 (25)	France	1	1.7	Grade I–II pRCC	5 Y	Yes
Carver BS, 2001 (24)	USA	1	1	RCC	4 Y	None
Penn I, 1995 (6)	USA	14	–	RCC	55 M	1[a]
Pliskin MJ, 1988 (23)	USA	1	2.7	RCCC	–	None

RCC, renal cell carcinoma without subtype pathology information; RCCC, renal clear cell carcinoma; pRCC, papillary renal cell carcinoma; –, information cannot be retrieved.
[a]The recurrent renal cancer was not donor original.

1971, Tunner reported a case in which a kidney with renal cell carcinoma was transplanted to an ESRF patient without resection of the tumor. The allograft kidney was largely destroyed by rejection, but the carcinoma continued to grow vigorously (29).

Discussion

In the present study, a systematic review of the literature identified 97 documented cases of transplantation of donor kidneys with SRC after tumor resection with only one possible recurrence. However, the presence of recurrence in this case is controversial because no progressive disease was detected and no biopsy of the lesion was performed. In addition, the lesion occurred nine yr after transplantation, whereas most renal cell carcinomas recur within two yr after surgery (30), and it was remote to the original lesion; therefore, it is reasonable to assume that the lesion was a de novo tumor rather than a recurrence. The cancer recurrence rate after partial nephrectomy (PN) in non-transplant patients with SRC is 1.47% (31). Therefore, current evidence suggests that the immunosuppressive condition after kidney transplantation is not likely to significantly increase kidney cancer recurrence. However, the transplantation of contralateral healthy kidneys from cadaveric donors with unilateral renal cancer is associated with a relatively high cancer recurrence rate at 4.8%. Further studies are needed to decrease the risk of cancer recurrence.

In addition to de novo renal tumors arising in allograft recipients, bilateral synchronous renal cancer and circulating tumor cells (CTCs) in donors are potential sources of risk for cancer dissemination and recurrence after transplantation of the contralateral kidney from cadaveric donors with unilateral renal cancer, whereas cancer multifocality is a risk for donor kidneys after resection of SRC. The possible presence of undetectable bilateral synchronous renal cancer in "healthy" contralateral kidneys needs to be considered. Therefore, a comprehensive evaluation should be performed before transplantation; furthermore, the use of donor kidneys with hereditary or papillary renal cell carcinoma is not recommended because of the high risk of bilateral cancer or multifocal cancer (32). Despite recent advances in the detection of CTCs, their identification is difficult in potential donors with renal cancer. Additional studies are required to further investigate CTCs in patients with renal cancer (33). Considering the relatively high rate of cancer recurrence associated with the transplantation of contralateral kidneys from cadaveric donor with unilateral renal cancer, the use of such donor kidneys is not recommended unless negative CTC has been confirmed by reliable methods.

Multifocality is associated with the risk of cancer recurrence in cases of allotransplantation of donor kidneys after resection of SRC. Although approximately 5.3% of SRCs are multifocal, only a small proportion can be detected by routine imaging examination (32). Therefore, more sensitive detection methods need to be developed and donor kidneys should be examined carefully before transplantation. Intraoperative ultrasound is more sensitive than preoperative ultrasound and CT for the detection of multifocal renal cancer (34), and it is therefore recommended in cases of kidney transplantation using SRC donors. Although we did not find studies reporting the detection of multifocal renal cancer by biopsy, pre-implantation or time-zero renal biopsy is currently recommended by many transplant surgeons to facilitate the selection of viable grafts and predict graft outcome. Furthermore, because pre-implantation or time-zero renal biopsy can theoretically increase the rate of detection of multifocal renal cancer, it should be performed routinely in cases of transplantation from SRC donors. In logistic regression models, significant predictors of multifocality of renal

cancer included male gender, family history of malignancy other than renal cell carcinoma, radiographic size of the lesion, histologic subtype other than clear cell, and Fuhrman grade IV (35). Therefore, the use of donor kidneys with certain evitable predictors of multifocality, such as family history of malignancy other than renal cell carcinoma, histologic subtype other than clear cell, and Fuhrman grade IV, should be avoided.

In kidney transplantation, tumor size and pathological grade should be graded according to the risk of donor-transmitted cancer. Nalesnik reported that the risk of donor-transmitted renal cancer after transplanting restored kidneys with SRC smaller than 1 or 2.5 cm was <0.1% or 1%, respectively (36).

The continuing development of immunosuppressants implies that the relationship between immunosuppressants and donor-transmitted cancer should be constantly re-evaluated. Among frequently used immunosuppressants, azathioprine and calcineurin inhibitors have been associated with post-transplant malignancies; mycophenolate mofetil has no impact on the incidence of malignancies, whereas targets of rapamycin inhibitors are associated with a lower incidence of malignancies (37). Rapamycin-based immunosuppressive therapy may be an optimal treatment for transplant patients using donor kidneys with SRC.

In cases of recurrence after renal transplant, the pattern of allograft renal cancer does not differ significantly from that of non-transplant patients. PN and microinvasive therapy are successful for the removal of allograft cancers detected at an early stage. However, locally advanced allograft cancer or metastatic disease is treated by allograft resection and immunosuppressant withdrawal. In patients with metastatic disease, rejection after immunosuppressant withdrawal results in complete regression of the tumor in approximately 50% of cases (6). Further studies are necessary to identify methods for strengthening the immune system to reject metastases after immunosuppressant withdrawal.

The present review was limited by the low level of evidence of the studies included and the scarcity of eligible trials. In addition, there is a potential for publication bias on this topic because successful stories are published more often than those describing unsuccessful outcomes of transplantation. Therefore, additional basic research and high-level evidence of clinical trials are necessary before kidneys from SRC donors can be used more extensively. In addition, a registry should be established in which all transplantation surgeries and procedures involving patients with SRC can be reported. The use of donor kidneys with incidental SRC during renal recovery or living donor evaluation may not be contraindicated if all related ethical issues are addressed appropriately.

Conclusions

In conclusion, despite the limited evidence, the present review suggests that the rate of cancer recurrence associated with kidney allotransplantation after resection of SRC is relatively low. Therefore, the implementation of well-designed clinical trials such as prospective cohort studies is warranted.

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