


# BMJ Open Efficacy and safety of stratified versus routine prophylaxis in living kidney transplantation from HBsAg+ donors to HBsAg- recipients: protocol for a multicentre, prospective, observational study

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## ABSTRACT

**Introduction** It remains unclear whether kidney transplantation (KT) from hepatitis B surface antigen (HBsAg) +donors to HBsAg- recipients (D(HBsAg+)/R(HBsAg-)) provides comparable transplant outcomes without hepatitis B virus (HBV) transmission compared with D(HBsAg-)/R(HBsAg-) KT. Moreover, no consensus has been reached for standardised prophylaxis regimens to prevent HBV transmission after D(HBsAg+)/R(HBsAg-) KT. We developed stratified prophylaxis regimens, including pretransplant antiviral treatment of donors, and pretransplant hepatitis B vaccination and post-transplant antiviral treatment of recipients, based on donors' and recipients' HBV serological characteristics. However, the safety and efficacy of stratified prophylaxis regimens remains unknown.

**Methods and analysis** We are conducting a prospective, multicentre, observational study. Between September 2020 and December 2023, 100 cases of (D(HBsAg+)/R(HBsAg-)) KT will be recruited from four university-affiliated hospitals with a follow-up at least 2 years. They will naturally receive stratified prophylaxis regimens or routine prophylaxis based on clinical experience to compare the efficacy and safety of these two regimens in (D(HBsAg+)/R(HBsAg-)) KT. The primary outcome will be post-transplant HBV infection to evaluate safety, defined as post-transplant HBsAg-→+ or HBV DNA-→+. The composite endpoint of prevention failure will be also an endpoint of safety (any one of HBsAg-→+, HBV DNA-→+, HB e antigen-→+, HB e antibody-→+ and HB c antibody-→+). The efficacy will be evaluated by transplant outcomes, including death-censored graft survival, patient survival, acute rejection, delayed graft function and kidney graft function.

**Ethics and dissemination** This study will be registered as a clinical audit at each participating hospital and has obtained approval from the Ethics Committee of West China Hospital (reference: 2020-683, 8 September 2020).

**Trial registration number** NCT04562051.

## Strengths and limitations of this study

- The prospective nature, large sample size, well-characterised data collection and the standardised study conditions are clear strengths of our study.
- This will provide robust evidence concerning HBV infection and transplant outcomes of HBsAg- recipients receiving living kidney transplantation from HBsAg+ donors. For recipients diagnosed with HBV infection after kidney transplantation, we will explore the associated risk factors.
- This study will be the first to establish stratified prophylaxis regimens for preventing donor-derived HBV infection in D(HBsAg+)/R(HBsAg-) kidney transplantation.
- A limitation is that routine prevention regimens vary slightly in different transplant centres, which might make it difficult to explain differences between stratified prevention and routine prevention.

## INTRODUCTION

Kidney transplantation (KT) is considered a preferred and cost-effective treatment for patients with end-stage renal disease (ESRD) compared with long-term dialysis therapy.<sup>1</sup> However, only a quarter of wait-listed patients have access to a deceased donor KT within 5 years annually due to ongoing severe organ shortages according to the United Network for Organ Sharing.<sup>2</sup> With the increasing number of candidates on the waiting list, the suitability criteria for donors have broadened over time. One extension is the application of KT from hepatitis B surface antigen (HBsAg) +donors to HBsAg- recipients [D(HBsAg+)/R(HBsAg-)].<sup>3-5</sup>

Although >240 million individuals worldwide present positive serological evidence of



HBsAg,<sup>6</sup> kidneys from HBsAg+donors are mainly allocated to matched HBsAg +recipients and seldom to HBsAg– recipients. Based on the British guidelines for KT, active hepatitis B virus (HBV) (HBV DNA >2000 IU/mL) in the donor is usually contraindicated for kidney donation due to concerns that HBsAg– recipients might be infected by HBV from allografts.<sup>7</sup> Importantly, posttransplant immunosuppressive therapy may modify the natural history of HBV, leading to progressive liver damage, including fulminant hepatitis and cirrhosis, and result in significant morbidity and mortality. Post-transplant HBV infection can adversely limit immunosuppressive agents, thereby increasing the risk of rejection events.

Regarding D(HBsAg+)/R(HBsAg–) KT, initial case reports present conflicting data, where some successfully demonstrated long-term stable kidney graft function without HBV transmission,<sup>8–10</sup> whereas others showed HBV-related complications.<sup>11–13</sup> In a subsequent cohort study with a median follow-up 38.7 months, only one patient developed de novo HBV infection in 58 recipients with HBs antibody (HBsAb) >10 IU/L, who received 400 U of hepatitis B immunoglobulin (HBIG) two times on the day of surgery and at 1-month post-transplant, with HBV status tested at 1, 3 and 6 months after D(HBsAg+)/R(HBsAg–) KT.<sup>3</sup> In another retrospective analysis, including 65 recipients with HBsAb >100 IU/L, no HBV prophylaxis provided similar transplant outcomes without HBV infection as those treated with lamivudine alone or lamivudine in combination with HBIG after D(HBsAg+)/R(HBsAg–) KT.<sup>4</sup> Our recent retrospective study indicated that HBc antibody (HBcAb)–/HBsAb– status of recipients is a risk factor of developing HBV infection and death, even if prophylaxis was adopted.<sup>5</sup> Therefore, for D(HBsAg+)/R(HBsAg–) KT candidates, sufficient natural or vaccine-acquired HBV immunity is recommended. Additionally, serum HBV DNA varies from undetectable level to several billion IU/mL, reflecting HBV-active status and prognosis. In our previous study, pretransplant donor HBV DNA positivity was an independent risk factor for the composite endpoint (defined as any HBV serology conversion, liver injury, graft loss or recipient death) in D(HBsAg+)/R(HBsAg–) KT recipients.<sup>14</sup> This suggests that direct exposure to HBV DNA +kidneys places recipients at a higher risk of acquisition of de novo HBV infection, and that recipients might need intensive prophylaxis regimens. However, that study was limited by its retrospective nature, small size and confounding and informational bias.

Another issue is that there is no standardised regimen capable of minimising the risk of postoperative HBV transmission in D(HBsAg+)/R(HBsAg–) KT. In the majority of cases, recipients receive intensive prophylaxis regimens based on clinical experience, including high-dose HBIG and/or long-term antiviral drugs.<sup>3 4</sup> Various prevention regimens increase the drug burden, reduce compliance and increase the difficulty of recipient management. Given the correlation between HBV transmission and the HBV virologic characteristics of donors and recipients, we

developed a stratified prophylaxis strategy, where intensive interventions are only used for those at high risk after D(HBsAg+)/R(HBsAg–) KT, including a pretransplant HBV DNA +donor and a recipient exhibiting low HBV immunity. In fact, stratified prevention has been adopted for D(HBsAg+)/R(HBsAg–) KT in our hospital; however, data on the efficacy and safety of stratified prevention are lacking.

According to Solid Organ Transplantation From Hepatitis B Virus-Positive Donors: Consensus Guidelines for Recipient Management,<sup>15</sup> there remain numerous clinical problems with D(HBsAg+)/R(HBsAg–) KT, including the following unanswered questions: (1) do HBsAb+recipients need preventive treatment; (2) what are the optimal prophylaxis regimens for HBsAb recipients; (3) what is the standardised strategy for regular HBV serological monitoring after transplantation and (4) what are the risk factors for donor-derived HBV infection? In the present study, we describe our plan to perform a multicentre, prospective, observational study enrolling 100 cases of D(HBsAg+)/R(HBsAg–) KT cases as the control group from four university-affiliated hospitals. The primary aim is to explore the efficacy and safety of stratified prophylaxis in D(HBsAg+)/R(HBsAg–) KT.

## METHODS

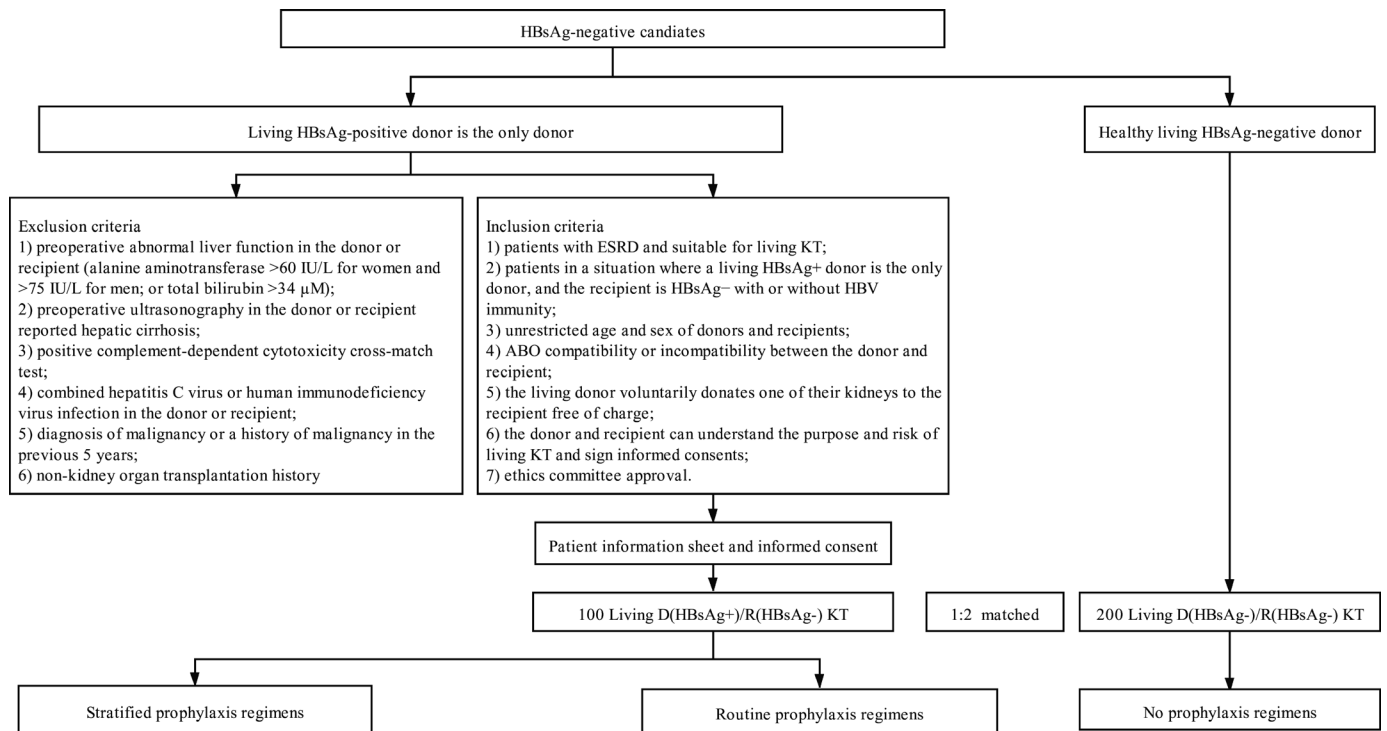
### Study design

This will be a prospective, multicentre, observational study registered at ClinicalTrials.gov.

### Study population

D(HBsAg+)/R(HBsAg–) KT is considered when living HBsAg+donors are only sources of kidney grafts than HBsAg– sources. We prospectively enrolled consecutive patients at four university-affiliated hospitals (patient-enrolment period: September 2020 to December 2023; full study duration: September 2020 to December 2025). All recipients are expected to be followed up for at least 2 years.

The inclusion criteria were as follows: (1) patients with ESRD and suitable for living KT, (2) patients in a situation where a living HBsAg +donor is the only donor and the recipient is HBsAg– with or without HBV immunity, (3) unrestricted age and sex of donors and recipients, (4) ABO blood-type compatibility or incompatibility between the donor and recipient, (5) the living donor voluntarily donates one of their kidneys to the recipient free of charge, (6) the donor and recipient can understand the purpose and risk of living KT and sign-informed consents and (7) ethics committee approval. The following exclusion criteria were also applied: (1) preoperative abnormal liver function in the donor or recipient (alanine aminotransferase >60 IU/L for women and >75 IU/L for men or total bilirubin >34 μM), (2) preoperative ultrasonography in the donor or recipient-reported hepatic cirrhosis, (3) positive complement-dependent cytotoxicity cross-match test, (4) combined hepatitis C virus or HIV infection in



**Figure 1** Study design. ESRD, end-stage renal disease; HBsAg, hepatitis B surface antigen; KT, kidney transplantation.

the donor or recipient, (5) diagnosis of malignancy or a history of malignancy in the previous 5 years and (6) non-kidney organ transplantation history (figure 1).

### Sample size estimation

In our previous study that enrolled patients from 1 January 2009 to 30 June 2017, 2071 living KTs were conducted, including 83 (4.0%) living D(HBsAg+)/R(HBsAg-).<sup>5</sup> After registration with Clinical Trials.gov and releasing the recruitment poster, the number of D(HBsAg+)/R(HBsAg-) KTs is expected to account for 5% of living KT cases. A total of 600–700 living KTs were performed in four centres annually. 100 cases of D(HBsAg+)/R(HBsAg-) KTs are expected to be performed from September 2020 to December 2023, with ~1782 cases of D(HBsAg-)/R(HBsAg-) KTs potentially conducted during the same period, of which 200 will be matched to the control group using propensity score-matching analysis.

### HBV prophylaxis regimens

100 D(HBsAg+)/R(HBsAg-) KT recipients will receive stratified prophylaxis based on the donors' and the recipients' HBV serological characteristics or routine prophylaxis based on clinical experience. No HBV prophylaxis will be adopted in D(HBsAg-)/R(HBsAg-) KT control group (figure 1).

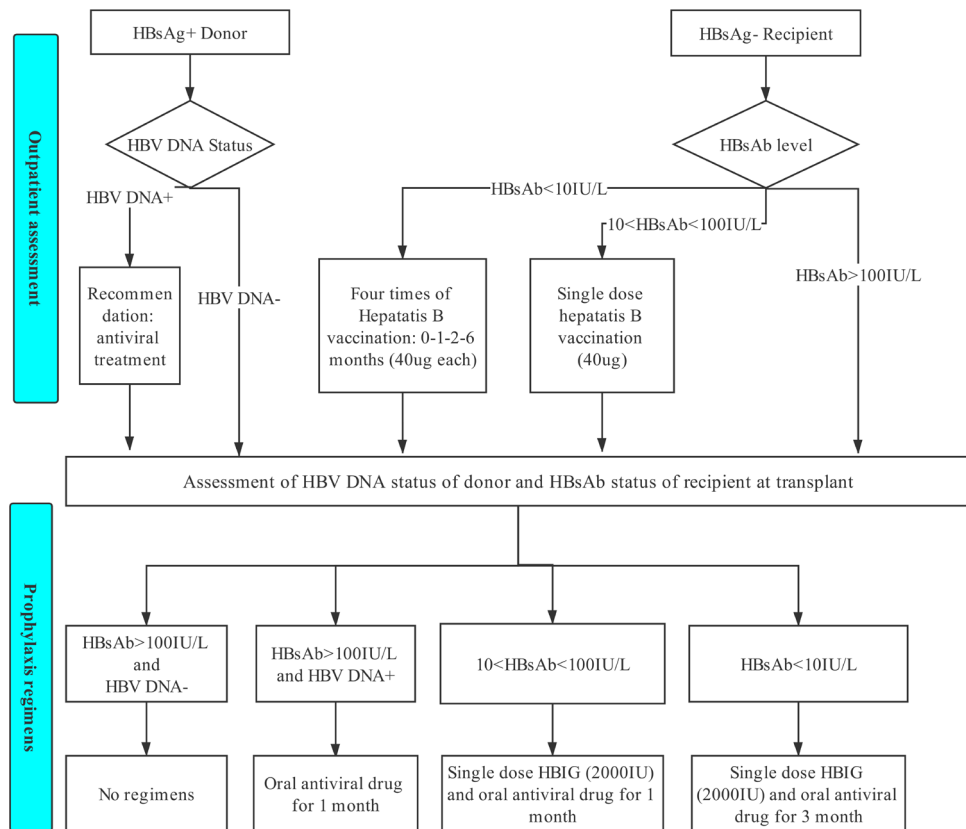
The process of stratified prophylaxis is shown in figure 2. Liver function, quantitative analysis of HBV DNA and serological markers of donors and recipients were examined at the first assessment. If the donor is HBV DNA+, HBV gene type and antiviral drug-resistance analysis are conducted, and antiviral treatments (entecavir as first-line therapy: 0.5 mg/day until transplantation)

are recommended. If recipient HBsAb level is <10 IU/L, 40 µg of HBV vaccine is inoculated each time according to the '0-1-2-6 months' procedure before transplantation. If HBsAb is between 10 IU/L and 100 IU/L, 40 µg of single-dose HBV vaccine is inoculated. After KT, recipients will receive stratified prophylaxis regimens based on preoperative donor and recipient HBV characteristics, as follows: (1) if recipient HBsAb level is >100 IU/L and the donor is HBV DNA-, the recipient receives no preventive measures, (2) if recipient HBsAb is >100 IU/L and the donor is HBV DNA+, the recipient receives antiviral treatment (entecavir as first-line therapy: 0.5 mg/day) for 1 month, (3) if recipient HBsAb is between 10 IU/L and 100 IU/L, the recipient is treated with a single dose of HBIG (2000 U) and antiviral treatment for 1 month, regardless of donor HBV DNA status and (4) if recipient HBsAb is <10 IU/L, the recipient receives a single dose of HBIG (2000 U) and antiviral treatment for 3 months, regardless of donor HBV DNA status.

In addition, transplant centres will adopt routine prophylaxis for D(HBsAg+)/R(HBsAg-) KTs based on clinical experience, including three doses of HBIG (2000 IU/dose) and antiviral drugs (entecavir as first-line therapy: 0.5 mg/day) for 6 months.

### HBV diagnostics and serological monitoring after KT

Measurements of HBsAg, HBsAb, HBe antigen (HBeAg), HBe antibody (HBeAb) and HBcAb were performed using a chemiluminescence microparticle immunoassay (Architect Qualitative System, Abbott, Germany). The HBV DNA quantitative test is estimated by using real-time PCRs (COBAS1 AmpliPrep/COBAS1 Taqman1; Roche



**Figure 2** Flowchart of stratified prophylaxis regimens. HBsAb, HBs antibody; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

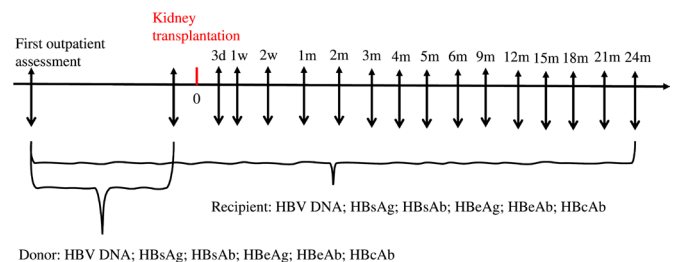
Diagnostics, Mannheim, Germany) with a dynamic range from 20 IU/mL to 170 000 000 IU/mL (sensitivity 99.8% and specificity 100%). For HBsAg- recipients receiving kidneys from HBsAg+ donors, quantitative analysis of HBV DNA and serological markers are routinely performed at first outpatient evaluation assessment, after vaccination and post-transplant 3 days, 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months, 12 months, 15 months, 18 months, 21 months and 24 months (figure 3). For the control group, quantitative analysis of HBV DNA and serological markers was performed only at pretransplant and post-transplant in the first year and second year or at the end of the study (table 1).

### Standard immunosuppression regimen

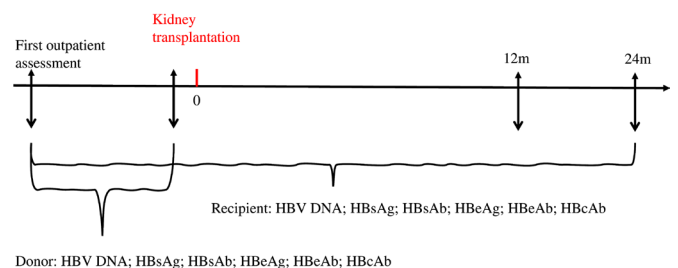
Standard immunosuppressive regimens include administration of mycophenolate mofetil (MMF) 1 day before the operation and tacrolimus on the second day after the operation with the dosage adjusted according to the tacrolimus trough level and serum MMF level. Recommended tacrolimus trough levels are 5 ng/mL to 10 ng/mL, and serum MMF levels are 30 mg/hour/L to 70 mg/hour/L. Induction therapies were selected according to the immunological risk of the recipients. Antithymocyte globulin (ATG) is used in patients at high immunologic risk (repeated KT, pretransplant panel reactive antibody level >20% or preoperative positive donor-specific antibody). An IL-2 receptor antagonist (Basiliximab) is used

in patients with low immunological risk. During and after transplantation, methylprednisolone will be injected intravenously daily, after which 60 mg prednisone will

**D(HBsAg+)/R(HBsAg-) KT: Stratified prophylaxis or routine prophylaxis**



**D(HBsAg-)/R(HBsAg-) KT: No prophylaxis**



**Figure 3** HBV monitoring regimen in D (HBsAg+)/R (HBsAg-) KT and D (HBsAg-)/R (HBsAg-) KT. HBsAb, HBs antibody; HBeAb, HB c antibody; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; KT, kidney transplantation.

**Table 1** Schedule of observations

| Visits                           | First outpatient assessment | Kidney Transplantation | 3 days | 1 week | 2 weeks | 1 month | 2 months | 3 months | 4 months | 5 months | 6 months | 9 months | 12 months | 15 months | 18 months | 21 months | 24 months |
|----------------------------------|-----------------------------|------------------------|--------|--------|---------|---------|----------|----------|----------|----------|----------|----------|-----------|-----------|-----------|-----------|-----------|
| Confirm eligibility              | ✓                           |                        |        |        |         |         |          |          |          |          |          |          |           |           |           |           |           |
| Informed consent                 | ✓                           |                        |        |        |         |         |          |          |          |          |          |          |           |           |           |           |           |
| Medical history                  | ✓                           | ✓                      | ✓      | ✓      | ✓       | ✓       | ✓        | ✓        | ✓        | ✓        | ✓        | ✓        | ✓         | ✓         | ✓         | ✓         | ✓         |
| Laboratory examination           | ✓                           | ✓                      | ✓      | ✓      | ✓       | ✓       | ✓        | ✓        | ✓        | ✓        | ✓        | ✓        | ✓         | ✓         | ✓         | ✓         | ✓         |
| Immunosuppressive regimen record |                             | ✓                      | ✓      | ✓      | ✓       | ✓       | ✓        | ✓        | ✓        | ✓        | ✓        | ✓        | ✓         | ✓         | ✓         | ✓         | ✓         |
| Adherence                        |                             | ✓                      | ✓      | ✓      | ✓       | ✓       | ✓        | ✓        | ✓        | ✓        | ✓        | ✓        | ✓         | ✓         | ✓         | ✓         | ✓         |
| Serum HBV characteristics        |                             |                        | ✓      | ✓      | ✓       | ✓       | ✓        | ✓        | ✓        | ✓        | ✓        | ✓        | ✓         | ✓         | ✓         | ✓         | ✓         |
| Transplant outcomes              |                             |                        | ✓      | ✓      | ✓       | ✓       | ✓        | ✓        | ✓        | ✓        | ✓        | ✓        | ✓         | ✓         | ✓         | ✓         | ✓         |

HBV, hepatitis B virus.

be used instead and gradually reduced to 5 mg/day to 10 mg/day for maintenance. The immunosuppressive regimen of each transplantation centre will be adjusted based on the standard immunosuppressive regimen.

### Data collection and study outcomes

Standard demographic, clinical and laboratory data will be prospectively collected from electronic medical records (table 1). These variables include age, sex, body mass index, medical history, ABO blood type, pretransplant and post-transplant HBV virologic characteristics and pretransplant and post-transplant kidney and liver function of recipients and donors. Specifically, HBV genotype, antiviral resistance and pretransplant treatment are also recorded for living donors. For recipients, native kidney diseases, relationship with the donor, history of organ transplantation, dialysis type and duration, human leucocyte antigen mismatch, panel reactive antibody level, ischaemic time, post-transplant prophylaxis regimens, immunosuppressive regimens and interest in clinical outcomes are collected. Recipients are advised to receive routine follow-up weekly in months 0 through 3, every 2 weeks in months 4 through 6, monthly from months 6 to 12, and every 3 months thereafter. The primary outcome is HBV infection of the recipient, defined as post-transplant HBsAg→+ or HBV DNA→+, which was used to evaluate safety. A composite endpoint of ‘prevention failure’ was also evaluated and defined as any one of HBsAg→+, HBV DNA→+, HBeAg→+, HBeAb→+ or HBcAb→+. Transplant outcomes included death-censored graft survival, patient survival, acute rejection and kidney graft function, which were used to evaluate efficacy. Other outcomes include liver function, surgical complications (delayed healing of incision, urinary fistula, urinary obstruction or vascular complications) and infection complications (urinary tract infection, lung infection or skin infection). Acute rejection (AR) was diagnosed clinically based on a significant increase in serum creatinine levels of 50% or more within 3 days, which was not explained by other reasons, including BK polyomavirus infection, cytomegalovirus infection and bacterial urinary tract infection, ureteral stricture and urinary stones. AR was confirmed by biopsy if necessary, and being treated primarily with bolus doses of methylprednisolone and with ATG if refractory.

### Statistical analyses

Baseline characteristics are described using descriptive analyses. Categorical variables are described as frequency and percentage and compared using the  $\chi^2$  test or Fisher’s exact test. Continuous variables are described as the mean±SD and compared using Student’s t test or analysis of variance. Univariate and multivariate logistic regression analyses are used to determine the risk factors for the primary outcomes. Cox regression analyses are performed to explore HBV-free survival. Graft and patient survival are analysed using the Kaplan-Meier method, and survival curves are compared using the log-rank test. Statistical

analyses are performed using SPSS (V.24.0) and SAS (V.9.2). A  $p < 0.05$  is considered significant.

### Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research. The results of this study will be made available to the public at [ClinicalTrial.gov](http://ClinicalTrial.gov).

### Ethics and dissemination

The study protocol and documents, including the consent form and participant information sheet, were approved by the Ethics Committee of West China Hospital (reference: 2020-683). The results will be published in a peer-reviewed journal and shared with the worldwide medical community.

### DISCUSSION

The use of kidneys from HBsAg+donors could safely expand the donor pool, as 3.5% of the global population presents serological evidence of HBsAg.<sup>5</sup> According to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors in 2017 (16), transplantation of kidneys from HBsAg +donors can be considered for HBsAg- recipients or recipients with HBV-protective immunity with informed consent of the recipient, possible antiviral HBV treatment of the recipient and post-transplant monitoring. On the one hand, this means that prospective studies with larger sample sizes are needed to confirm the safety and efficacy of D(HBsAg+)/R(HBsAg-) KT. On the another hand, it is necessary to establish standardised prophylactic regimens.

Previous studies encouraged transplant programmes from HBsAg D(HBsAg+)/R(HBsAg-). Jiang *et al* first reported clinical outcomes of a large series of D(HBsAg+)/R(HBsAg-) KTs after enrolling 65 HBsAb +recipients and using 308 HBsAb + recipients of kidneys from HBsAg- donors as the control group.<sup>3</sup> After transplantation, recipients with HBsAg or HBsAg +donors received 400 U HBIG once and two times, respectively. After a median follow-up of  $38.4 \pm 15.4$  months, only one patient developed de novo HBV infection in each group (1.5% vs 0.3%). In particular, seven HBsAb +recipients from HBV DNA +donors received intensive prophylaxis regimens, including 400 U HBIG weekly for 3 months and 100 mg/day lamivudine for 6 months; however, no de novo HBV infection or liver injury was observed. That study suggested that transplantation of kidneys from HBsAg+donors might be considered for HBsAg- recipients with HBV protective immunity. A subsequent cohort study by Chanchaonthana *et al* compared KT outcomes between HBsAg- recipients with HBsAb  $>100$  mIU/mL undergoing KT from HBsAg +donors ( $n=43$ ) and HBsAg- donors ( $n=86$ ). They found no statistical difference in graft and patient survival between the two groups ( $p=0.43$  and  $p=0.50$ , respectively) after a median follow-up of 58.2 months and

no markers of HBV infection, including HBsAg or HBcAb (de novo), or HBV DNA detected in the HBsAg +donor group.<sup>4</sup> An important finding was that recipients undergoing KT from HBsAg +donors with no HBV prophylaxis ( $n=20$ ) provided comparable outcomes with those treated with lamivudine alone ( $n=21$ ) or in combination with HBIG ( $n=2$ ). However, both studies were unable to explore the risk factors for de novo HBV infection due to their small sample size; therefore, it remains unclear how HBsAb levels of recipients and the HBV DNA viral load of the donors influence clinical outcomes.

Our recent study reported outcomes of D(HBsAg+)/HBV DNA- or +/R(HBsAg-) living KT recipients with or without HBV immunity after enrolling 83 HBsAg- recipients and using 384 D(HBcAb+)/R(HBcAb-) patients as the control group. Before KT, 24 donors (28.9%) were HBV DNA+, 20 recipients were HBsAb- and all 83 recipients received HBV prophylaxis (18, HBIG alone; 41, antivirals alone and 24, both) in the D(HBsAg+)/R(HBsAg-) group.<sup>5</sup> After a median follow-up of 36 months, two of 83 (2.41%) D (HBsAg+)/R (HBsAg-) recipients and one of the 384 (0.26%) D (HBcAb+)/R (HBcAb-) patients became HBsAg+ ( $p=0.083$ ). Univariate analysis revealed that a pretransplant HBsAb-/HBcAb- combination in the D (HBsAg+)/R (HBsAg-) recipients carried a significantly higher risk of HBsAg- $\rightarrow$ + ( $p=0.027$ ) and death ( $p=0.027$ ). However, due to potential selection, recall and confounding bias, the impact of prophylaxis regimens has not been explored, and multivariate analysis could not be conducted because of the limited sample size. Another unanswered question is how pretransplant antiviral treatment of donors influences clinical outcomes. Therefore, this ongoing prospective, multicentre study will present an important finding relevant to KT.

Current clinical evidence suggests that donor-derived HBV transmission is rare in pretransplant recipients with HBsAb  $>10$  IU/L.<sup>16</sup> It is suggested that recipients of D (HBsAg+)/R (HBsAg-) KT be vaccinated with the hepatitis B vaccine, especially HBsAb- recipients. Unfortunately, the seroconversion rate after vaccination is often lower in patients with chronic kidney disease than in healthy adults due to impaired innate and adaptive immunity. Lin *et al*<sup>17</sup> showed that 48.6% of patients still presented negative HBsAb after vaccination (20 mg vaccine), and that only 27.7% of patients presented HBsAb  $\geq 100$  IU/L. Within 12 months after transplantation, 25% of recipients will lose their protective antibody, especially those with HBsAb  $<100$  IU/L before transplantation.<sup>18</sup> Therefore, in our stratified regimen, a 40 mg hepatitis B vaccine is recommended in order to increase the response rate. Second, the virologic characteristics of donors are related. HBsAg- recipients might be at a higher risk of HBV transmission when the donor has a higher viral load. In our previous study, the incidence of donor-transmitted HBV infection was numerically higher in recipients receiving a kidney from a donor with HBV DNA  $>1000$  IU/mL (4.2%) as compared with a HBV DNA  $<1000$  IU/mL (1.7%), despite of the prophylactic

regimens.<sup>5</sup> Therefore, we developed stratified prophylaxis regimens that might be more scientific and accurate for the prevention of HBV infection and representing a more reasonable allocation of medical resources. However, no research data have been reported on the efficacy and safety of this regimen. In the initial research design, we planned to conduct a multicentre, prospective, non-inferiority clinical trial to compare the efficacy, safety and cost-effectiveness between stratified prevention and routine prevention. According to our previous results, the incidence of the composite endpoint was estimated to be 22% in the reference group,<sup>5</sup> and the treatment group proportion is assumed 27% under the null hypothesis of inferiority. The power was computed for the case when the actual treatment group proportion was 14%, and the test statistic used was the one-sided Z-test. A sample size of 107 in the stratified group and 107 in the routine group achieved 80.058% power to detect a non-inferiority margin of difference under the null hypothesis of 0.05; however, an insufficient sample forced us to change the research design. Finally, we conducted a prospective observational study.

In the control group, prophylaxis was not adopted. A previous study showed a significantly low infection rate of HBcAb +kidney grafts as compared with that of liver allografts.<sup>19</sup> A review of 1385 HBsAg-/HBcAb +kidney donations showed that HBsAg seroconversion was reported in only four cases (0.28%; 95% CI 0.006 to 0.57),<sup>20</sup> with similar results reported in our previous work that included 384 recipients receiving D(HBsAg-/HBcAb+) R(HBsAg-/HBcAb-) KT. Despite the lack of prophylaxis, only one patient developed HBsAg+.<sup>5</sup> Therefore, it is difficult to demonstrate the benefits of antiviral prophylaxis or vaccination given such a low risk of de novo infection.

Regarding de novo HBV infection, recent studies show that HBV mutations, although rare, are possible and can potentially confer resistance to HBIG or antivirals, suggesting a higher risk of donor-derived HBV transmission.<sup>21</sup> Additionally, both adaptive and innate immune responses are important for controlling HBV infection. Chen *et al.*<sup>22</sup> reported anti-T cell antibodies as independent risk factors for HBV reactivation in 322 HBsAg-/HBcAb+patients after KT (p=0.002). Therefore, T cell-depleting agents (eg, ATG) as induction therapy might place recipients at a higher risk of HBV infection. Moreover, B-cell-depleting agents might increase the risk of reactivation and HBV infection. In a retrospective cohort study that included 172 HBsAg-/HBcAb+recipients receiving ABO-incompatible KT, rituximab was associated with higher HBV infection rates (p=0.009).<sup>23</sup>

This study has several strengths and limitations. The multicentre, prospective nature and large sample size are clear strengths. Furthermore, a clinical study comparing stratified prophylaxis regimens and routine prophylaxis regimens has never been performed on HBsAg- recipients receiving kidneys from HBsAg +donors, and we have demonstrated a well-characterised data collection. A

limitation is that routine prevention regimens vary slightly in different transplant centres, which might make it difficult to explain differences between stratified prevention and routine prevention.

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**Contributors** XW, TL, HL, WS and HZ were the initiators of this study; XW and SY wrote this protocol; XW, SY, TS, ZH, YF, XL conducted this study procedures and tool part in the data acquisition; all authors took part in the study planning; SY and XW wrote the final manuscript and all authors read and approved it.

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**Data availability statement** After publication, data are available upon reasonable request. A proposal with a detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Participant data will be provided after approval from the corresponding author.

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