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CKJ REVIEW

Assessment of hypertension in kidney transplantation by ambulatory blood pressure monitoring: a systematic review and meta-analysis

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ABSTRACT

Background. Hypertension (HTN) is common following renal transplantation and it is associated with adverse effects on cardiovascular (CV) and graft health. Ambulatory blood pressure monitoring (ABPM) is the preferred method to characterize blood pressure (BP) status, since HTN misclassification by office BP (OBP) is quite common in this population. We performed a systematic review and meta-analysis aimed at determining the clinical utility of 24-h ABPM and its potential implications for the management of HTN in this population.

Methods. Ovid-MEDLINE and PubMed databases were searched for interventional or observational studies enrolling adult kidney transplant recipients (KTRs) undergoing 24-h ABP readings compared with OBP or home BP. The main outcome was the proportion of KTRs diagnosed with HTN by ABPM, home or OBP recordings. Additionally, day–night BP variability and dipper/non-dipper status were assessed.

Results. Forty-two eligible studies (4115 participants) were reviewed. A cumulative analysis including 27 studies (3481 participants) revealed a prevalence of uncontrolled HTN detected by ABPM of 56% [95% confidence interval (CI) 46–65%]. The pooled prevalence of uncontrolled HTN according to OBP was 47% (95% CI 36–58%) in 25 studies (3261 participants). Very few studies reported on home BP recordings. The average concordance rate between OBP and ABPM measurements in classifying patients as controlled or uncontrolled hypertensive was 66% (95% CI 59–73%). ABPM revealed HTN phenotypes among KTRs. Two pooled analyses of 11 and 10 studies, respectively, revealed an average prevalence of 26% (95% CI 19–33%) for masked HTN (MHT) and 10% (95% CI 6–17%) for white-coat HTN (WCH). The proportion of non-dippers was variable across the 28 studies that analysed dipping status, with an average prevalence of 54% (95% CI 45–63%).

Conclusions. In our systematic review, comparison of OBP versus ABP measurements disclosed a high proportion of MHT, uncontrolled HTN and, to a lesser extent, WCH in KTRs. These results suggest that HTN is not adequately diagnosed and controlled by OBP recordings in this population. Furthermore, the high prevalence of non-dippers confirmed that circadian rhythm is commonly disturbed in KTRs.

Keywords: ambulatory blood pressure monitoring, hypertension, kidney transplantation, meta-analysis, systematic review

INTRODUCTION

Arterial hypertension (HTN) is a highly prevalent complication among kidney transplant recipients (KTRs) [1] and is a major contributing factor to graft failure and cardiovascular (CV) morbidity and mortality [2, 3] in this population. HTN is a modifiable risk factor and well-controlled blood pressure (BP) associates with longer transplant and patient survival [4–6].

The diagnosis and clinical decisions about the treatment of HTN in the transplant population have traditionally been based on measurements of BP in the clinic setting. However, office BP (OBP) has important limitations in diagnosing HTN because of its intra- and inter-individual variability [7], thus misclassifying a proportion of KTRs [8, 9]. Furthermore, it has been shown that nighttime BP, rather than isolated OBP readings, correlates better with markers of vascular damage [i.e. carotid intima-media thickness (IMT)] [9] and morbid CV events [10, 11] in these individuals. Nocturnal [9], masked (MHT) [12] and white-coat HTN (WCH) [13] are all common in this population.

Current recommendations by the National Institute for Health and Care Excellence (NICE) [14] and the American US Preventive Services Task Force [15] recommend that in individuals with high-normal OBP at high risk of developing CV disease, the diagnosis of HTN be confirmed with ambulatory BP monitoring (ABPM). However, the use of this technique remains scarcely applied in KTRs, a population notoriously at high risk for CV disease [1–3].

Since diagnostic biomarkers should be specifically tested in the population where they are applied in clinical practice, we conducted a systematic review and meta-analysis aimed at comparing the prevalence of KTRs diagnosed with uncontrolled HTN by 24-h, daytime and/or nighttime ABPM, home BP and OBP.

Additionally, we collected data from studies reporting day–night BP variability and assessment of dipper/non-dipper status in the same population.

MATERIALS AND METHODS

We performed this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] and published the protocol of the meta-analysis [17]. Due to the length of the originally planned systematic review and meta-analysis, we decided to split it into two different systematic reviews. Thus, some prespecified outcomes reported in the aforementioned protocol (i.e. association between BP recordings and renal and CV outcomes) will be mentioned in a second manuscript.

Data source and search strategy

We searched Ovid-MEDLINE and PubMed databases for articles without time or language restriction through 16 November 2020 using focused, high-sensitive search strategies (Supplementary data, Table S1). Bibliographies of relevant studies and reviews were screened for additional articles. The search was designed and performed by two authors (A.Pisano and D.B.).

Study selection and data extraction

Any interventional [randomized and non-randomized controlled trials (RCTs) or uncontrolled trials] or observational study (prospective or retrospective study) dealing with the reference population undergoing 24-h ABP readings compared with traditional clinic or home BP measurements was included. Studies enrolling adult KTRs from either live or deceased organ donors were included. Studies where at least part of the

population fulfilled the above criteria were included in the review. Studies were excluded if they: (i) did not include KTRs; (ii) did not compare 24-h ABPM with at least one of the traditional OBP or home BP measurements; (iii) did not provide data on the outcomes of interest. We aimed at comparing the agreement of different BP measurements in diagnosing HTN and assessing the relation between BP recordings by different methods in KTRs.

The main outcome of interest was assessment of proportion of KTRs diagnosed with uncontrolled HTN by 24-h, daytime and/or nighttime ABPM, home or OBP recordings. Pre-specified additional outcomes were day–night BP variability and assessment of dipper/non-dipper status.

Two investigators (A.Pisano and D.B.) independently screened titles and abstracts, excluding studies not pertinent to the topic, and assessed the retrieved full texts to determine eligibility according to the pre-specified inclusion/exclusion criteria. A third reviewer (C.Z.) solved possible discrepancies on study judgements. Reviews, editorials, letters, case reports and studies performed on children or adolescents (age <18 years) were excluded, but screened for additional references. If more than one article from a single study was identified, eligible data from all reports were considered, but each study was included only once. Data extraction was performed by one Author (A.Pisano), using a customized table (see Supplementary data, Table S2). The following properties were extracted from each study: study characteristics (first author, year of publication, country, design and inclusion/exclusion criteria), population characteristics (number of patients, age, sex, body mass index, baseline renal function, transplantation vintage, baseline OBP, ABPM and home BP), comorbidities [diabetes, HTN, left ventricular hypertrophy (LVH), coronary heart disease and heart failure], and BP thresholds according to OBP, ABPM and home BP recordings.

Data analysis

The pooled HTN prevalence with 95% confidence intervals (CIs), by, respectively, ABPM and home BP/OBP methods, was obtained by aggregating single-study prevalence.

To avoid selection bias, studies not involving a random population sample (i.e. studies that selected fully uncontrolled and/or controlled hypertensive subjects by OBP) were not included in the pooled analysis. Nevertheless, in order to maximize information, prevalence data produced by the above studies were reported narratively.

Data were pooled using the random-effects model and, to guarantee robustness of the model, we also analysed data with the fixed-effects method. The χ^2 test on N − 1 degrees of freedom, with an alpha of 0.05 considered for statistical significance, and the Cochrane-I^2 [18] were used to assess the presence of heterogeneity. I^2 values of ≤25, <50 and >50% were assumed to correspond to low, medium and high levels of heterogeneity, respectively. Values ≥75% correspond to a highly significant heterogeneity across studies with a strong effect in the pooled estimate of the outcomes. Possible sources of heterogeneity were explored performing sensitivity and subgroup analyses according to different BP metrics and/or BP thresholds. Meta-regression analyses were performed for identifying possible effect modifiers in meta-analyses including at least 10 studies.

Publication bias was investigated by Egger's regression test and by visual inspection of funnel plots.

Data analyses were performed by two authors (A.Pisano and G.D.) using Stata/IC (version 13.1, StataCorp LP, College Station, TX, USA), and independently verified by a third author (C.Z.).

RESULTS

Search results

Figure 1 shows the flow diagram of the study selection process. Nine hundred and seven potentially relevant references were initially found. Four additional citations were added by personal search. By screening titles and abstracts, 765 citations were excluded for various reasons (search overlap, study population/clinical problem not pertinent and review articles). Among the 146 studies selected for full text examination, 95 were excluded due to studying other populations or not reporting outcomes of interest ($n = 20$), lack of a comparator group ($n = 60$), being review articles ($n = 4$) or any other reason ($n = 11$).

A total of 51 articles referring to 42 studies (4115 participants) were finally included in the review.

Study characteristics

Study design. The vast majority of the reviewed studies had an overall observational design, including three retrospective studies [8, 19, 20], 20 prospective studies [21–40], 14 studies with a cross-sectional design [7, 12, 13, 41–51] and one survey [9]. Four studies had an interventional design [52–55], of which three were RCTs [52, 53, 55]. Only 4 [7, 29, 34, 48] out of 42 studies compared ABPM with both the traditional OBP and home BP measurements.

BP categories considered in the various studies. The overwhelming majority of studies enrolled uncontrolled hypertensive KTRs (being treated with antihypertensive medication), except two studies [12, 40] that involved apparently controlled hypertensive individuals, and one additional study [21] that included normotensive stable KTRs not treated with antihypertensive drugs. The final population analysed in this review included 4115 patients and the range of patients enrolled in

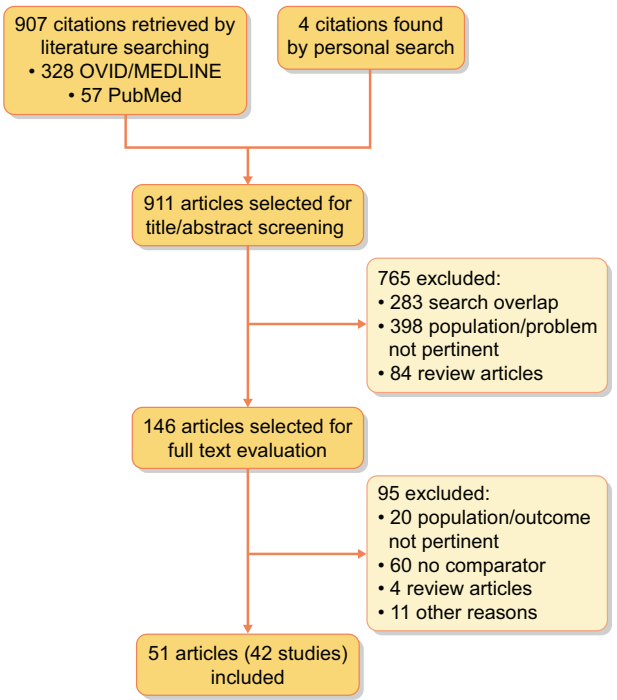

FIGURE 1: Study selection flow.

these studies was extremely variable, spanning from 10 [52] to 868 [13] individuals.

Criteria adopted for the definition of HTN according to OBP and 24-h ABPM. Overall, the classification of patients as hypertensive by OBP readings in these studies was based on contemporary documents issued by the 1996 World Health Organization (WHO) [56] and/or Reports of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP (JNC 6–7) [57, 58]. Definition of arterial HTN for the general population by these documents was office systolic BP (SBP) exceeding 140 mmHg or diastolic BP (DBP) exceeding 90 mmHg, and/or use of antihypertensive drugs. The European Society of HTN/European Society of Cardiology (ESH/ESC) 2013 guidelines (SBP ≥140 mmHg and/or DBP ≥90 mmHg or treatment with hypotensive drugs) [59] were adopted by six studies [9, 33, 36, 39, 47, 51]. Five studies [8, 13, 38, 43, 49] set office HTN diagnosis threshold at 130/80 mmHg, in accordance with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [60].

In one study [50], office HTN was defined as mean office SBP ≥140 mmHg and/or mean office DBP ≥90 mmHg, according to the JNC 8 report [61].

Standardized OBP readings (measured by the same nurse/technician, a mean of 3 times after at least 10 min of quiet resting in a semi-recumbent position), adhering to WHO [56] and/or ESH/ESC recommendations (3–5 min of rest in a sitting position) [59], were carried out with a mercury sphygmomanometer in 21 studies [12, 19, 22–25, 27–29, 31, 34, 36, 37, 40, 42, 48, 51–55], whereas an automated oscillometric device was used in 10 studies [7, 9, 13, 30, 32, 33, 35, 39, 43, 47]. Not standardized (taken manually by different people or in a single reading) OBP measurements were performed by five studies [8, 21, 38, 45, 50]. Six studies [20, 26, 41, 44, 46, 49] reported no information on clinic BP methodology.

In four studies [7, 29, 34, 48] focusing on home BP, patients (354 participants) were considered hypertensive when the mean reading of self-measured BP taken several times during the day for 5–7 days (12–28 valid measurements) [7, 34, 48] exceeded 135/85 mmHg, i.e. the threshold recommended by the ESH/ESC 2003 guidelines [62, 63]. In one study, home BP was measured on a single day only with four measurements per patient [29].

Classification of patients as hypertensive by ABPM, following the ESH/ESC 2003 recommendations (24-h ABP >125/80 mmHg), was adopted by eight studies [7, 26, 27, 29, 30, 32, 43, 54]. In the majority of the studies, arterial HTN was recognized in accordance with ESH/ESC 2013 guidelines if 24-h ABPM exceeded the target set at 130/80 mmHg. Target diurnal and nocturnal BP in these studies were set at 135/85 and 120/70 mmHg, respectively [8, 9, 33, 35, 36, 38–40, 47, 49, 50, 55]. Five studies [19, 24, 41, 45, 51] defined HTN as 24-h ABPM >135/85 mmHg, daytime BP >140/90 mmHg or nighttime BP >120/80 mmHg [64]. Paoletti *et al.* [31] and Marcondes *et al.* [25] defined HTN as an average BP ≥130/80 mmHg according to the criteria issued by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines on HTN and Antihypertensive agents in CKD [65]. Two studies [12, 34] defined HTN according to the JNC 7 criteria (mean ABP >140/90 mmHg).

Mostly, ABPM technology used an automated cuff with an oscillometric device conforming to the advancement of medical instrumentation recommendations (i.e. Spacelabs 90207) with BP readings taken at 15- and 30-min intervals throughout the day and night, respectively [7, 9, 13, 19, 22, 23, 25, 26, 28–31, 33, 39, 40, 42, 45, 47–49, 52–54]. Twenty-four-hour recordings were carried out every 30 min during the day and every 60 min during the night in six studies [21, 37, 43, 49, 51, 55]. Other devices and customized analytical software were used in other studies [12, 24, 27, 32, 34–38, 41, 50, 51]. No information on ABPM methodology was provided by three studies [8, 44, 46].

Nocturnal BP dipping was calculated as the difference between mean daytime and mean nighttime BPs. Patients were classified as dippers if mean BP decreased by 10% or more during the nighttime period.

The main characteristics of the studies reviewed are described in Supplementary data, Table S2.

In-study and pooled prevalence of HTN by ABPM, home and OBP

Overall, the single-study prevalence of uncontrolled HTN by ABPM and OBP ranged from 19% [35] to 95% [31] and from 3% [36] to 95% [31], respectively. Studies that selected fully uncontrolled [43, 48, 52, 54, 55] or controlled hypertensive subjects [12, 40] by OBP were excluded from the cumulative analysis of uncontrolled HTN prevalence detected by OBP recordings.

Prevalence of HTN according to daytime and nighttime ABP was variable, spanning from 26% [9] to 87% [49] and 21.6% [54] to 84% [50], respectively.

Only two [7, 29] out of four studies [7, 29, 34, 48] reported information about the prevalence of HTN according to home BP. Among 183 KTRs, Agena *et al.* [7] observed a prevalence of uncontrolled HTN of 56.3, 36.1 and 44.8%, respectively, by OBP, ABPM and home BP. In the study by Stenehjem *et al.* [29], OBP, ABPM and home recordings revealed uncontrolled HTN in 47, 84 and 71% of patients, respectively.

Overall, 29 studies [7–9, 12, 13, 19, 22, 24, 26–33, 35, 36, 38–40, 42, 44, 45, 47, 49–51, 54] with randomly recruited subjects provided suitable data on the in-study prevalence of uncontrolled HTN by ABPM and/or OBP and were included in pooled meta-analyses.

A cumulative analysis of 27 studies (3481 participants) [7–9, 12, 13, 19, 22, 26–33, 35, 36, 38–40, 44, 45, 47, 49–51, 54] based on ABPM exposed a high heterogeneity (97.4%). The cumulative prevalence of uncontrolled HTN by this technique was 56% (95% CI 46–65%, $\chi^2 = 988.41$, $P = 0.00$, $I^2 = 97.4\%$) (Figure 2). Sensitivity analyses, stratifying by different ABPM metrics (24 h or daytime; Supplementary data, Figure S1, $\chi^2 = 816.71$, $P = 0.00$, $I^2 = 97.5\%$ and $\chi^2 = 146.66$, $P = 0.00$, $I^2 = 96.6\%$, respectively), different BP thresholds (ESH/ESC 2003, $\chi^2 = 138.83$, $P = 0.00$, $I^2 = 95.7\%$ or ESH/ESC 2013 guidelines, $\chi^2 = 560.68$, $P = 0.00$, $I^2 = 97.7\%$ or other thresholds, $\chi^2 = 211.03$, $P = 0.00$, $I^2 = 97.6\%$) (Figure 2) or type of devices used (Spacelab or other devices; Supplementary data, Figure S2, $\chi^2 = 858.58$, $P = 0.00$, $I^2 = 98.1\%$ and $\chi^2 = 96.97$, $P = 0.00$, $I^2 = 92.8\%$, respectively) did not reduce the high heterogeneity observed in the cumulative analysis.

Visual inspection of the funnel plot and Egger's regression test ($P = 0.12$) indicate that the presence of publication bias was unlikely (Supplementary data, Figure S3a).

As for OBP, the cumulative prevalence (25 studies, 3261 participants) of uncontrolled HTN was 47% (95% CI 36–58%) [7–9, 13, 19, 26–33, 35, 36, 38, 39, 42, 44, 45, 47, 49–51]. Again there was considerable heterogeneity among the various studies ($\chi^2 = 1349.18$, $P = 0.00$, $I^2 = 98.2\%$). Heterogeneity remained high in sub-analyses carried out according to different BP thresholds (KDIGO or ESH/ESC 2013 guidelines or others) (Figure 3) or type of devices (Supplementary data, Figure S4; mercury sphygmomanometer, $\chi^2 = 674.61$, $P = 0.00$, $I^2 = 98.8\%$; automatic

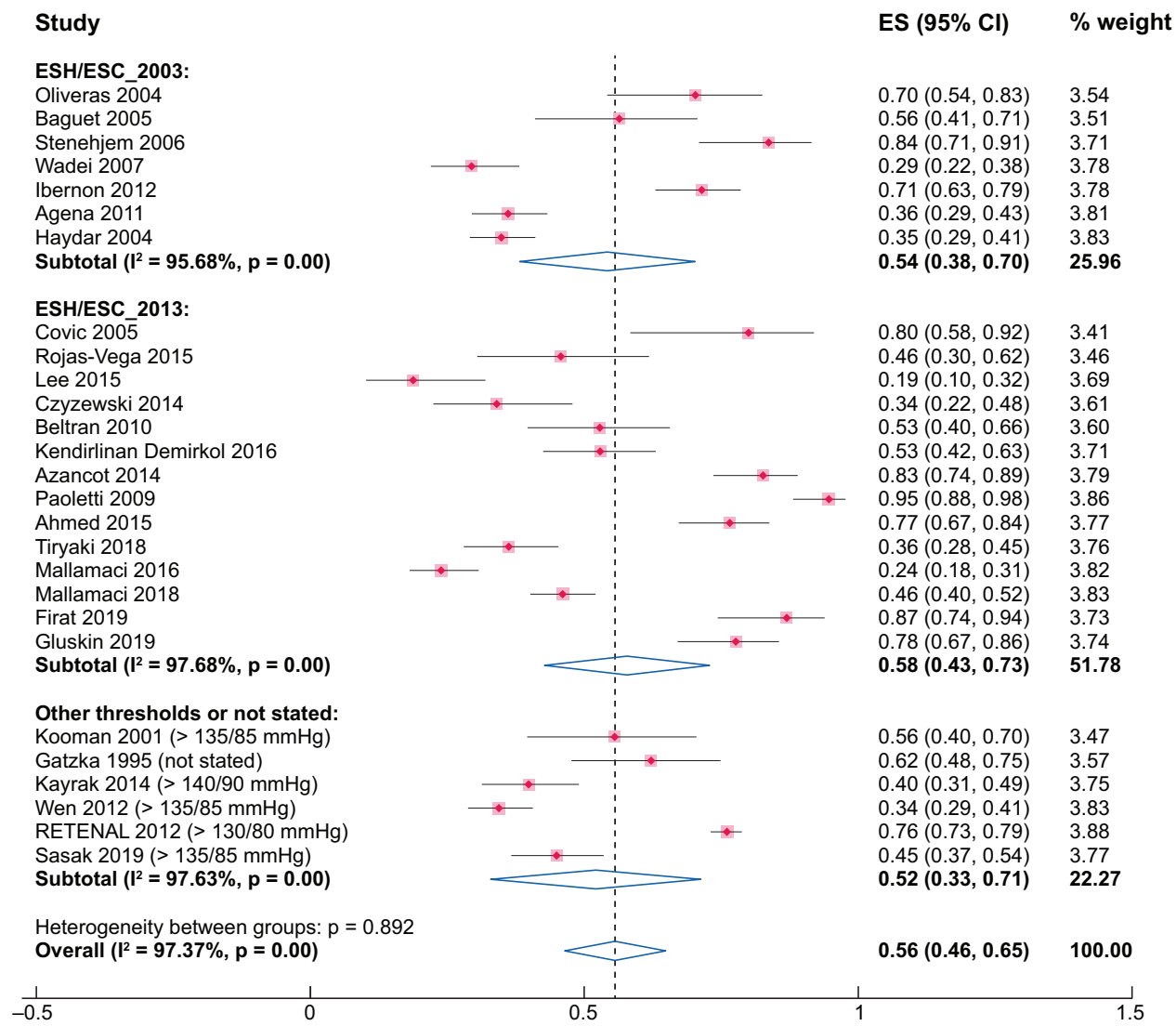

FIGURE 2: Pooled prevalence of uncontrolled HTN by ABPM. Sensitivity analysis stratifying by different BP thresholds (ESH/ESC 2003 or ESH/ESC 2013 or other guidelines).

oscillometric devices, $\chi^2 = 479.76$, $P = 0.00$, $I^2 = 98.3\%$; not standardized or unreported methods, $\chi^2 = 44.18$, $P = 0.00$, $I^2 = 94.5\%$).

Visual inspection of the funnel plot and the Egger's regression test ($P = 0.36$) show absence of publication bias (Supplementary data, Figure S3b).

BP profile by different methods

Four studies compared BP profiles by ABPM, home BP and OBP recordings. In general, OBP and home BP were higher than ABPM but the results were not homogeneous [7, 29, 34, 48].

In 183 KTRs, Agena *et al.* [7] found both office and home SBP higher than ABPM values, whereas DBP was lower by home and higher by OBP when compared with ABPM. In 49 KTRs with early deterioration in graft function, Stenehjem *et al.* [29] observed morning and evening home BP significantly higher than 24 h, daytime ABP and OBP ($P < 0.001$ for all), and no difference between OBP and ABPM values.

In 49 KTRs enrolled by David *et al.*, no significant difference between awake and, respectively, home and office SBP was observed, whereas daytime DBP resulted lower ($P < 0.05$) than the corresponding OBP and home values [34].

The vast majority of the studies comparing OBP versus ABPM, reported overall higher values by OBP than ABPM [13, 23, 25–27, 30, 32, 36–38, 40, 41, 45, 52, 53, 55]. Only six studies (349 participants) [8, 20, 21, 28, 49, 50] recorded lower OBP than 24-h ABPM. No significant difference between OBP and ABPM recordings (24-h, daytime and nighttime BP) was found in 11 studies (965 participants) [9, 19, 22, 24, 31, 33, 35, 39, 42, 46, 47].

Steigerwalt *et al.* [43] reported that patients receiving tacrolimus ($n = 20$) had higher OBP than ABPM values while those receiving sirolimus ($n = 18$) had higher ABPM than OBP values.

Concordance rate among methods

Agreement in the diagnosis of controlled and uncontrolled HTN. Agreement amongst different BP measurements in classifying patients as controlled or uncontrolled hypertensive were reported in 17 studies [7, 8, 13, 19, 23, 24, 26, 29, 32–35, 38, 41, 45, 47, 51], with variable concordance rate among studies, spanning from 39% [8] to 90% [35]. A pooled analysis including data from

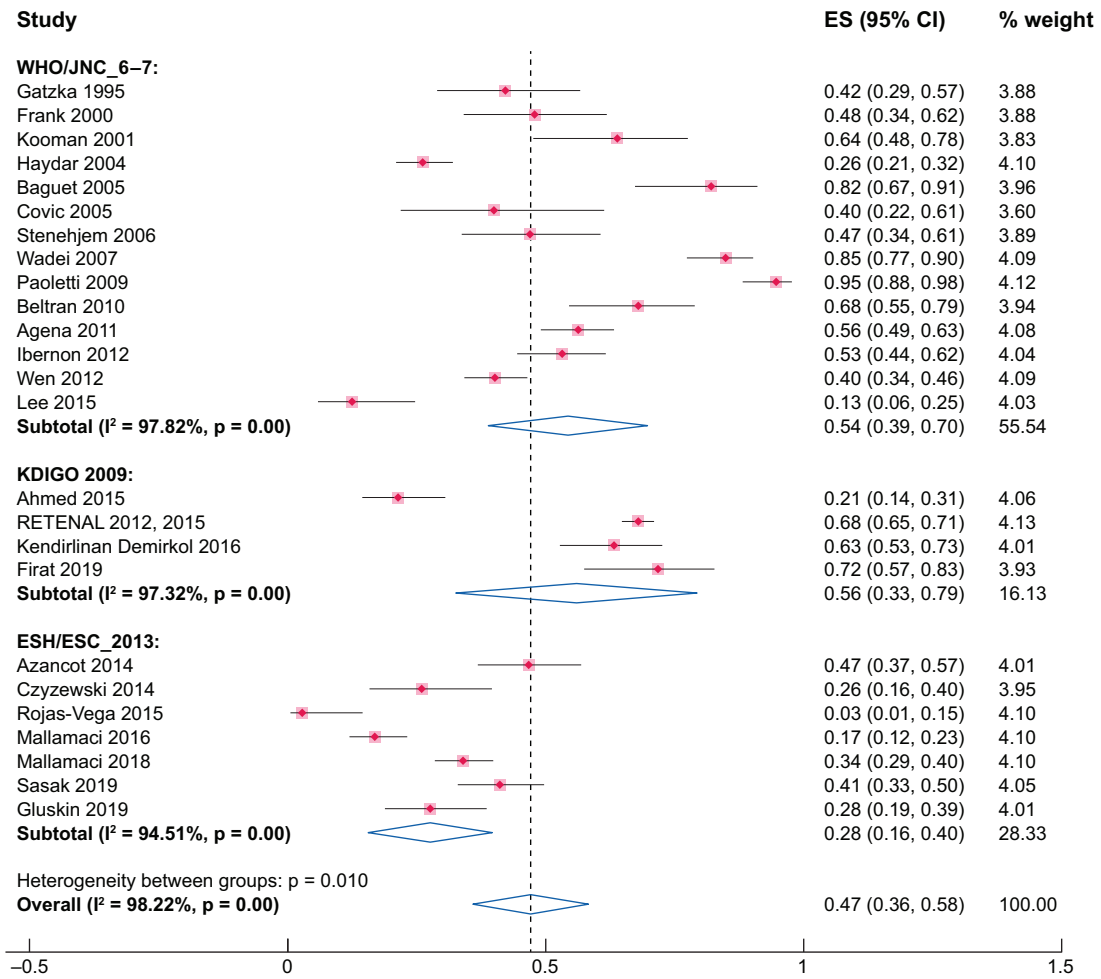

FIGURE 3: Pooled prevalence of uncontrolled HTN by OBP. Sensitivity analysis stratifying by different BP thresholds (WHO/JNC 6–7 or KDIGO 2009 or ESH/ESC 2013).

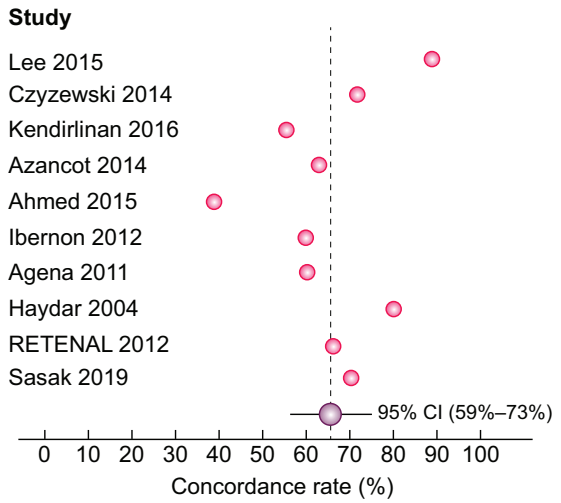

FIGURE 4: Concordance rate between ABPM and OBP in diagnosing controlled and uncontrolled HTN.

10 studies [7, 8, 13, 26, 32, 33, 35, 38, 47, 51] revealed an average prevalence of the agreement of 66% (95% CI 59–73%) (Figure 4).

Nominally significant correlations between OBP and 24-h ABPM were also reported by five studies (all comparisons, $r = 0.46$–0.69, $P < 0.05$ to $P < 0.001$) [19, 24, 29, 41, 45]. No correlation between methods was found by Jacobi *et al.* [23].

Using receiver operating characteristics curve analyses, Agena *et al.* [7] reported a significant but unsatisfactory diagnostic concordance of OBP (61.2%) with ABPM (the gold standard) and a higher diagnostic concordance with home BP (72.7%). David *et al.* [34] found OBP more specific than home BP in diagnosing HTN (98% versus 89% specificity) as defined by ABPM. In contrast, home BP was superior to OBP in identifying patients achieving the BP goal (83% versus 50% specificity) defined on the basis of ABPM.

OBP–ABP discordance in diagnosing uncontrolled HTN. ABPM gave information on HTN phenotypes among KTRs, revealing a considerable disagreement with OBP. Thirteen studies [8, 12, 13, 26, 32, 33, 35, 38–40, 47, 50, 51] addressed the OBP-24-h ABP discordance, finding a variable proportion of MHT, spanning from 6% [35] to 58% [8], and WCH ranging from 0% [47] to 24.7% [38].

Two cumulative analyses of 11 and 10 studies, respectively, revealed an average prevalence of 26% (95% CI 19–33%) for MHT and 10% (95% CI 6–17%) for WCH (Figure 5). Meta-regression analyses did not reveal any association between the prevalence of MHT ($P = 0.12$) and WCH ($P = 0.065$), respectively, and the severity of renal impairment [mean estimated glomerular filtration rate (eGFR)].

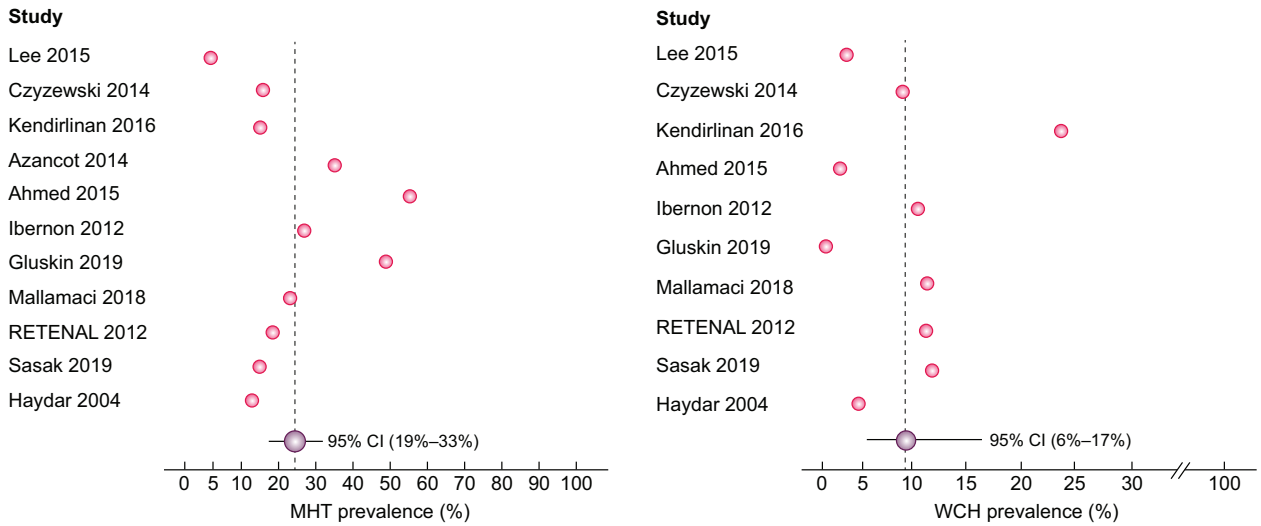

FIGURE 5: Average prevalence of MHT and WCH.

Nominally, MHT was common among patients with apparently controlled HTN, according to OBP, with a prevalence of 36 and 40% in two surveys by Tiryaki *et al.* [40] and Kayrak *et al.* [12], respectively. Similarly, in a cross-sectional study involving 92 stable KTRs, 36% of patients had MHT and no patient had WCH [47]. A high discordance (61%) between OBP and ABPM emerged also in a study by Ahmed *et al.* [8]. In this study, 58% of patients had MHT and more than a half of this proportion (33%) resulted from isolated nocturnal HTN. Conversely, an overall lower disagreement (20%) was observed in the study by Haydar *et al.* [26].

In a longitudinal study by Mallamaci *et al.*, with an average follow-up of 3.9 years, in ∼37% of outpatient visits, OBP measurements provided indications for changes in antihypertensive therapy discordant from those by 24-h ABPM [66]. In detail, in 12% of all visits, OBP provided a wrong indication to HTN treatment (OBP >140/90 versus 24-h ABPM <130/80 mmHg), whereas in 25% of all visits, it failed to correctly indicate the need of starting or intensifying HTN treatment (OBP <140/90 versus 24-h ABPM >130/80 mmHg).

Circadian BP pattern

Prevalence of abnormal dipping status. Overall, 28 studies [9, 12, 13, 19, 22–33, 35, 37, 38, 41, 43–47, 50, 51, 54] assessed the percentage of nocturnal dipping. Among these, 10 studies [13, 19, 28–32, 35, 37, 50] reported variable proportion of patients with a reverse dipping pattern (i.e. an actual BP rise during nighttime), spanning from 14% [13] to 42% [19]. The proportion of non-dippers was variable across studies, ranging from 8.1% (non-diabetic KTRs without LVH) [46] to 85% (hypertensive KTRs receiving tacrolimus) [43].

A cumulative analysis including 28 studies revealed an average prevalence of non-dipping of 54% (95% CI 45–63%), thus confirming that circadian rhythm is commonly disturbed in KTRs. Meta-regression analysis did not reveal any association between prevalence of non-dipping status and the mean eGFR (P = 0.25).

Kooman *et al.* [19] reported a nocturnal decrease of 0.42 ± 11.7 (range –35 to 22) mmHg for SBP and 2.3 ± 6.2 (range –10–10) mmHg for DBP. Using the criterion of a ≥10% SBP decrease during sleep defining normal day-to-night BP variability (dipping), a high proportion of non-dippers (94.5%) was observed; among these, 41.6% were reverse dippers.

Gatzka *et al.* [22] reported a mean nighttime fall of 9 ± 8 mmHg with respect to daytime values, classifying 51% of patients as non-dippers. Stratifying patients according to transplantation vintage in early (130–210 days, $n = 15$), intermediate (211–348 days, $n = 15$) and late (356–598 days, $n = 15$) transplant patients, the dippers percentage increased with the time after transplantation (27% versus 47% versus 73%, respectively), thus reducing the proportion of non-dippers. The more time had passed since KT, the higher was the fall of BP during sleep ($r = 0.38$, $P < 0.01$).

In line with this finding was a study by Covic *et al.* [28]. Defining normal circadian rhythm (dipping status) as a sleep-to-awake ratio >0.92 for SBP and >0.90 for DBP, at 1-month post-transplantation 100% of patients were complete non-dippers (including 80% reverse dippers), whereas, after >1 year, the proportion of non-dippers decreased to 60%, among which 20% were reverse dippers.

Wadei *et al.* [30] observed 24% of dippers (ΔSBP 13.7 ± 3.8%), 42% non-dippers (ΔSBP 5.2 ± 2.4%) and 34% reverse dippers (ΔSBP −9.1 ± 8.4%). A high proportion of non-dippers, 67.8% [38] and 73% [25], respectively, was observed in two different studies.

A study by Sasak and Ecder [51] recorded different proportions of non-dippers among sustained normotensive (24.1%), WCH (29.4%), MHT hypertensive (31.8%) and sustained-hypertensive patients (25%). Gluskin *et al.* [50] observed a non-dipping BP pattern in 73% of patients and such an alteration was associated with tacrolimus use (P = 0.020). Among 76 KTRs, the rates of BP dipping, non-dipping and reverse dipping patterns were 26.7, 53.3 and 20%, respectively. Stenehjem *et al.* [29] observed 82% of non-dippers, according to SBP; among these patients, 39% were reverse dippers. In the RETENAL study [13], there was a high proportion of non-dippers (48%), including 34% of reverse dipper patients.

In a survey by Mallamaci *et al.* [9], including 172 stable KTRs, 36% of patients had a night–day ratio ≥1, indicating a non-dipping pattern. In a prospective study including 126 kidney recipients followed-up for a mean of 45 ± 11 months [32], 51.5% of patients were classified as non-dippers and 31.1% as reverse dippers.

DISCUSSION

In this systematic review in KT patients, we found a prevalence of uncontrolled HTN of 56% with ABPM and 47% with OBP, and a 44% discordance for the definition of uncontrolled HTN among the two techniques. Thus, in a population at high CV risk like KTRs, ABPM exhibited a considerable disagreement with OBP, revealing a high prevalence of MHT and the non-dipping pattern. The results of this review provide a basis for extending to transplant patients recommendations by NICE [14] and the American US Preventive Services Task Force [15] that the diagnosis of HTN is confirmed with ABPM.

Post-transplant HTN is multifactorial in nature and immunosuppressive drugs, renal transplant artery stenosis, recurrent renal disease, genetic factors, recipient's native kidney, as well as poor-quality donor kidney all contribute to the high prevalence of HTN in this population [4]. The renal transplant population is a peculiar chronic kidney disease (CKD) population [67], characterized by the chronic use of immunosuppressive drugs and by a history of CKD and dialysis treatment of variable length in most cases.

Previous studies in CKD patients reported a prevalence of WCH ranging from 2% to 41% [68–75] and of uncontrolled MHT ranging from 6% to 51% [68–70, 72–76]. Furthermore, the non-dipping phenomenon, including actual nocturnal HTN, is progressively more frequent at more severe degrees of renal dysfunction [77] and the global prevalence of this alteration ranges from 14% to 75% [69, 70, 74, 75, 77–84]. Importantly, out-of-office BP is superior to OBP for the prediction of CKD progression in pre-dialysis CKD patients and CV outcomes in both pre-dialysis and dialysis patients [68, 70, 71, 74, 85–100]. As remarked, due to the poor diagnostic performance of OBP, both NICE [14] and the American US Preventive Services Task Force [15] recommend ABPM to confirm the diagnosis of HTN if clinic BP is between 140/90 mmHg and 180/120 mmHg, a recommendation based on a thorough literature review and cost–benefit analysis. Such a recommendation is valid for the general population and there are reasons to believe that it should be perhaps applied with more stringency to patients at high risk of CV events [101]. In our meta-analysis, the average prevalence of uncontrolled MHT (26%) was higher than that in a meta-analysis of six studies in CKD patients (8.3%) [102]. In CKD patients, WCH [103] does not pose any excess risk for adverse outcomes, while MHT predicts a 50% and 77% risk excess for CV and kidney outcomes, respectively. Thus the high prevalence of MHT in transplant patients, which is higher than in CKD patients, is of peculiar clinical relevance in this population. We believe that the risk of misdiagnosing HTN by OBP among renal transplant patients is such that the application of ABPM or home BP (if ABPM is not tolerated) for confirming HTN cannot be omitted. HTN is the most relevant modifiable risk factor for CV disease in renal transplant patients and well-controlled BP associates with longer transplant and patient survival [4–6].

Possibly, targeting nocturnal HTN may reduce the high risk for CV events in transplant patients. The prevalence of nocturnal uncontrolled HTN in 172 treated KTRs was as high as 67% [9]. Such an alteration is robustly associated with IMT, underlying a severe degree of atherosclerosis. Furthermore, a reverse dipper pattern emerged as a risk factor for CV events in a prospective study including 126 kidney recipients followed up for a mean of 45 ± 11 months [32]. These observations replicate in a specific population (renal transplant population) findings in the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) study [104], a study in the community where the association between nighttime BP and death and CV events was stronger than that of daytime, 24 h ABPM and clinic BP with the same events.

The 2012 KDIGO BP Guideline in CKD did not provide evidence-based recommendations regarding the use of ABPM to evaluate BP in CKD patients, including renal transplant patients [105]. The issue was reconsidered in the 2021 update of the same guidelines [106]. In these guidelines, the recommended method for HTN diagnosis and monitoring is standardized BP measured by automatic recorders [as in the SPRINT (Systolic Blood Pressure Intervention Trial) study [107]]. The authors of these guidelines remarked that in many regions of the world, home BP or ABPM is impractical to be systematically recommended in the CKD population. However, this remark may not apply to renal transplantation. Renal transplantation is a complex, multi-specialty intervention usually delivered in hospitals with adequate human and instrumental resources. Even though we could not make any formal comparison between HTN as detected by standardized BP measurements (SPRINT study approach) and 24-h ABPM, other studies showed that standardized BP has a scarce agreement with 24-h ABPM [108, 109]. Therefore, we believe that the systematic application of the recommendation by NICE and the American US Preventive Services Task Force is also valid for confirming the diagnosis of HTN in high-risk population like transplant patients.

The high heterogeneity of the estimates of HTN prevalence by ABPM and OBP limits the value of the cumulative estimates of this alteration in the transplant population. This phenomenon is not unique to the transplant population. A high heterogeneity was detected also in meta-analyses focusing on the prevalence of HTN in hospital patients [110] or pre-hypertensive subjects [111] or treatment-resistant patients [112]. The prevalence of MHT [113] and WCH [114], two phenotypes common among renal transplant patients, is also very heterogeneous.

In conclusion, MHT, altered circadian BP profile and nocturnal HTN are frequent in KTRs and might contribute to the high renal and CV risk of these patients. These data suggest that the current recommendation by transplant guidelines to diagnose and monitor HTN exclusively by traditional BP measurements may need to be reconsidered.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

All authors participated in the critical revision of the article for important intellectual content. F.M., J.-M.H., A.Persu, G.W., P.S., M.B., A.O., C.J.F., N.K., B.S., G.L., P.R., L.V., I.N.B. and C.Z. contributed to the study concept and design. A.Pisano and D.B. developed and ran the search strategy, and were responsible for data acquisition, interpretation and analysis. G.D. contributed to the data analysis. C.Z. and A.Pisano drafted the manuscript.

BOX 1. Definitions

MHT	Normal OBP but elevated out-of-clinic BP values
WCH	High OBP but normal out-of-clinic BP values
Controlled HTN	Optimal BP targets (OBP <140/90 and ABP <130/80 mmHg) in people with HTN (treated with antihypertensive medication)
Dipping	Normal circadian BP variation (physiological nocturnal BP drop >10% of daytime)
Non-dipping	Abnormal circadian BP variation, defined as <10% reduction in BP during sleep
Reverse dipping	Abnormal circadian BP variation, defined as nocturnal BP rise

CONFLICT OF INTEREST STATEMENT

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