Author’s response to reviews

Title: Ambulatory monitoring unmasks hypertension among kidney transplant patients: Single center experience and review of the literature

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Author’s response to reviews:

See also attached file

April 14, 2019

Dear Editor,

We are grateful for the opportunity to improve our manuscript in light of the reviewers’ comments and submit it for your further evaluation. Below we address the reviewers’ comments point-by-point.

Sincerely,

Iddo Ben-Dov, MD, PhD
Swapnil Hiremath (Reviewer 1): Gluskin et al report on a single centre study with some data on ABPM in 76 kidney transplant recipients. They report a very large discrepancy between clinic and ABPM and report an association between this difference and tacrolimus use.

One wonders if the method of clinic BP can explain these results - because these are dramatically different than the reported literature

We concur with the reviewer’s notion – however, these were real-life office blood pressure measurements, reflecting real-life clinical practice.

Introduction:

- The 2017 ACC guidelines are really the ACC/AHA guidelines –

Fixed

- The JNC8 guidelines are a misnomer. The last JNC guidelines were JNC 7 (read the title carefully) JNC got out of the guideline business, hence the 2017 ACC/AHA guideline

The report is titled: “2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8)” . Thus, we changed “JNC8 guideline” to “JNC8 report”.

- It may be useful to mention that the KDIGO rec is a 2D recommendation

Done

- The authors cite the ESC/ESH guidelines later in results: why not cite them in introduction too?

Done

Methods:

What were the criteria for doing ABPM in kidney transplant patients? Were these consecutive 76 patients? What made the authors stop at that number? Did some patients not consent?

These were indeed 76 consecutive consenting patients. Some patients did not consent. The study was performed as part of the first author’s MD thesis, in which a preliminary sample size analysis suggested that 80 patients are required (now updated in the Methods section).

From table 1, the vintage of patients seem to be a few years out after transplant. Is this true?
Yes, with the reported variability. Patients less than 3 months from transplantation were excluded.

What monitor (oscillometric) was used by the nurses?

Either of 2 identical mobile Welch Allyn monitors (52000 series) was used. We added this information in the Methods section.

how often, and whether was this oscillometric device as well as the aneroid device calibrated?

Devices were investigated/calibrated according to manufacturers’ recommendations (2 years for oscillometric devices and 6 months for aneroids).

Results:

Table 1: how many patients had clinic BP measured by oscillometric versus aneroid?

The numbers were 16 and 60, respectively (now noted in the Results).

Table 4/5: can method of clinic BP be added to the list of covariates?

Done (Table 5, not statistically significant)

Hassan N Ibrahim, MD, MS (Reviewer 2): I read with interest the manuscript titled "Ambulatory monitoring reveals widespread underestimation of blood pressure among kidney transplant patients: Single center experience and review of the literature" by Gluskin and colleagues. The manuscript analyzes the concordance between clinic and 24-hour ambulatory measurements among 76 kidney transplant recipients.

General comments:

Originality and Novelty: This manuscript addresses a "Call to Action" by several European scientific societies to describe clinic and ambulatory BP patterns as well as clinic-aware differences in kidney transplant recipients. While not an original idea, this study significantly enhances the scant literature in this genre. The authors should be commended for evaluating the interval hourly averages to examine the association/interaction between BP and medication dosing.

Scientific Soundness: No significant issues related to study design. Single center observational study with a comparison to the international literature.
Major issues for the authors to address:

1. Ambulatory BP monitoring
   a. 15 measurements of a 24-hour ABPM seems too small a number of measurements. By my estimation, if the protocol measurements are every 20 minutes during the day and every 30 minutes during nighttime sleep, then 15 total measurements are representative of less than 25% of expected readings. In our clinic, we would deem these ABPM invalid and repeat the study. While the minimum number of ABPM measurements is not an agreed upon standard, the European society recommends a minimum of 70% of expected readings with 20 daytime measurements and 7 nighttime measurements. I would recommend repeat analysis with this minimum definition.

   Of course – the minimum number of valid measurements was 20 awake and 8 sleep measurements. We regret the mistake.

2. Results
   a. Table 5: The authors highlight a significant association between immunosuppressant medication use and differences in systolic blood pressures. However, 72% of patients are taking tacrolimus compared with 18% cyclosporine and 10% on non-CNI based therapy. Are these results adjusted for population differences or unadjusted?

   The analysis method was indeed appropriate for the unbalanced rate of immunosuppressant regimens.

Minor issues for the authors to address:

1. Methods:
   a. Clinic BP measurements: The authors describe clinic blood pressure measurements as "an average of 2-3 visits". Were the individual clinic blood pressures single or averages of at least three measurements taken 5 minutes apart?

   The individual clinic blood pressure levels typically reflected single measurements. This information now appears in the Methods section.

   b. Further, of the oscillometric device measurements, were these observed or unobserved?

   These were observed measurements – now included in the Methods description.
2. Results

a. Table 1: For ease of visibility, recommend changing sex, smoking, and type of allograft to percentiles. Listing both male and female sex seems redundant, recommend listing only one. Same issue with type of allograft.

Done

b. Line 210-211: What is significance of non-dipping of heart rate? Are the implications the same or different as non-dipping blood pressures? Please clarify.

There are additive prognostic implications. We refer the reviewer to a previous manuscript from our larger cohort (reference #50 in the revised manuscript).


By “referring nephrologist” we mean the patient’s nephrologist, which also participated in the patient’s recruitment and occasionally consenting process. We omitted this sentence in the revised manuscript.

3. Limitations

a. The authors imply but do not state the word measurement bias among clinic blood pressures. I recommend inserting the term "measurement bias".

We are not sure what the reviewer means by “measurement bias” as there are several possible biases related to the measurement process.

b. There is no control group in this study. How does these results compare with non-kidney transplant chronic kidney disease populations?

We did include a referred patient control cohort for perspective, and review the clinic-ambulatory blood pressure difference in CKD populations in the Discussion.

Lastly, I think the focus of the paper should change to highlight the huge prevalence of masked hypertension in this population which is overlooked often.

We now place greater emphasis on this issue in our Title and Discussion.