Author's response to reviews

Title: Prevalence and Predictors of Resistant Hypertension in Primary Care
Setting: A cross-sectional study

Authors:

YookChin Chia (chiayc@um.edu.my)
SiewMooi Ching (sm_ching@upm.edu.my)

Version: 4 Date: 31 May 2014

Author's response to reviews: see over
May 18, 2014

Journal Executive Editor
BMC Family Medicine
BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom

Dear Prof Rupert Payne,

REVISED PAPER FOR PUBLICATION: Ref. MS: 3220873321101514

Title: Prevalence and predictors of Resistant Hypertension in a Primary Care Setting:

A cross-sectional study by Chia Yook Chin a,b (MBBS, FRCP) Ching Siew Mooi (MD, MMed Fammed)

Thank you to you and the other reviewer for your feedback. I have addressed and made the necessary changes and revisions according to your comments point by point

I have also done the revisions and changes directly onto our main manuscript and below are the changes highlighted in blue which I have made.

I also enclose the full revised manuscript.
With warm regards,

Thank you,

Yours sincerely
Dr Chia Yook Chin
Department of Primary Care Medicine,
Faculty of Medicine,
University of Malaya,
50603 Kuala Lumpur,
MALAYSIA

Fax +603-7957 7941

Email: chiayc@um.edu.my
Reviewer's report (Prof Rupert Payne)

Thank you very much for all your pertinent comments. I have made the revisions as below.

Abstract

1. Results - the odds ratios for age and BMI are not interpretable - they should state "per year of age" (rather than having this in the conclusions) and "per kg/m2"

*We have now removed the sentences “Hypertensive patients who are obese and have underlying chronic kidney disease are associated with higher odds of having resistant hypertension. On the other hand, increased in one year of age is associated with lower odds of having resistant hypertension in this population“ from the conclusion section, and have expanded the conclusion as below (please see number 2).*

*In the result section, we have now interpreted the odds for age, BMI and CKD and have added “per year of age” to read as*

In multivariate logistic regression analysis, presence of chronic kidney disease is more likely to be associated with resistant hypertension (odds ratio [OR] 2.89, 95% confidence interval [CI] 1.56-5.35). On the other hand, increase per year of age is associated with lower odds of resistant hypertension in this population (OR 0.96, 95% CI 0.93-0.99).

2. Conclusions - some interpretation, such as implications for health service policy, would be useful as a final sentence.

*We have now added and expanded the sentence in conclusion to read as*

Resistant hypertension is present in nearly one in ten hypertensive patients on treatment. Hypertensive patients who have underlying chronic kidney disease are
associated with higher odds of having resistant hypertension. Hence, in managing patients with hypertension, primary care physicians should be more alert and identify patients with chronic kidney disease as they are more likely to develop resistant hypertension. By doing that, these patients can be treated more aggressively earlier in order to achieve blood pressure target.

Background

3. It is mentioned that little is known about prevalence of resistant hypertension in primary care. However, I would suggest that it is worth expanding this to say there is little known about resistant hypertension in the south east Asian population - this is surely what sets the current work aside from studies of resistant hypertension elsewhere. The authors might like to comment on why this is important - is hypertension viewed as a specific growing problem in this part of the world for example?

*Thank you for the suggestion. We have now edited the sentences in background to read as*

Strokes are more common in Asia than in developed countries while the reverse is true for coronary artery disease [20]. Elevated BP is one of the most important risk factors for stroke [21] and poorly controlled hypertension increases this risk [3, 22, 23]. Hypertension is of particular importance in South East Asia because while the prevalence of hypertension in Asian countries is nearly the same as that of most developed countries [24] bit many more patients in Asia with hypertension are not controlled to target [25]. For example in developed countries the control rates of hypertension was around 52%[26] to 60%[27] but it is as low as 26% in Malaysia[28]. Resistant hypertension is one of the contributors of uncontrolled hypertension. Little is
known about the prevalence of resistant hypertension in the South East Asian population. Hence we wanted to examine prevalence of resistant hypertension in treated hypertensive patients in a South East Asian country to ascertain its contribution to uncontrolled hypertension.

Methods

4. Setting - further information should still be added to clarify who the population included in the study are. Is this a general population sample? Or is it restricted in some way - for example, ability to pay for health care, need for specialist hypertension care, etc? Many readers who are unfamiliar with the Malaysian health system will be uncertain as to exactly what part of the population is being studied.

*We have added further information to clarify who the population included in this study are.*

The study was conducted in an outpatient clinic of the University Malaya Medical Centre, a teaching hospital in Kuala Lumpur, the capital city of Malaysia. This clinic is run by 14 family medicine specialists, 30 vocational trainees in family medicine and other medical officers. This tertiary hospital including its primary care clinic serves a multi-ethnic population of 450,000 in the surrounding area.

People in the community can choose their own source of care. This teaching hospital functions on an open access basis to the community. A full range of services are offered at this clinic. Those who attend our clinic are mainly those requiring long term care for chronic conditions like hypertension, diabetes and dyslipidaemia in addition to the usual short term primary care illnesses.
Care is provided free for public sector service employees and their dependents while all others are required to pay an equivalent of US$8.50 for both the consultation and a month’s supply of medication.

5. Data collection - there is still insufficient information about BP measurement, to allow the reader to draw conclusions about the robustness of the BP measurements:

i) the authors should be explicit about who measured BP. Was it carried out by a researcher? Or was it carried out as part of routine clinical care?

*We have added this sentence in the data collection to read as*

Patients’ blood pressures which were measured by the attending doctors routinely as part of the daily routine care were also captured from the medical records

ii) was BP taken from a single measurement? Or was it from repeated measurements either i) at a single point in time, or ii) from different points in time. Guidelines often advise that a diagnosis of hypertension is confirmed by 3 separate measurements, around a week apart. If this was not the case, it should be made clear to the reader and acknowledged in the limitations.

Patients who were recruited into our study were those who had been diagnosed to have hypertension or were on antihypertensive medications. Diagnosis of hypertension in our clinics is made in accordance to standard recommendations i.e. based on at least 2 BP measurements at least 2 weeks apart [3].

6. statistical analysis - mention is made of ethnicity as an independent variable the classification of this should be given in the preceding section on data collection.

*We added the classification of ethnicity in the method section under setting to read as*
The study population consists of three main ethnicities which are Malays, Chinese and Indians [29].

Results

7. Multivariable logistic regression - there are a number of areas that raise concern:

i) Although the authors state in the methods how variable selection was conducted, it is hard to see how "clinically significant" was defined – surely gender, dyslipidaemia and smoking, which are all excluded from the multivariable model, could all be considered clinically significant?

*Based on univariate analysis all these variables (gender, dyslipidaemia, smoking) were not significant and hence we did not include them into our multivariate logistic regression analysis. However as suggested by you, we have now included these variables (ie gender, dyslipidaemia and smoking) into the multivariate logistic regression and this has changed the BMI from significant to not significant.*

So now only age and CKD remain significant and not BMI. We have now included these (extra) variables and stated our new findings in Table 3.

Table 3 Predictors of resistant hypertension at UMMC (N=1217)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR*</th>
<th>95% C.I.</th>
<th>P=value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>2.89</td>
<td>1.562 - 5.345</td>
<td>0.001**</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m2 increase)</td>
<td>1.05</td>
<td>0.994 - 1.102</td>
<td>0.080</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>0.96</td>
<td>0.928 - 0.988</td>
<td>0.007**</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.88</td>
<td>0.511 - 1.511</td>
<td>0.640</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malays</td>
<td>1.30</td>
<td>0.638 - 2.633</td>
<td>0.474</td>
</tr>
<tr>
<td>Chinese</td>
<td>1.20</td>
<td>0.618 - 2.339</td>
<td>0.587</td>
</tr>
<tr>
<td>Indians</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.01</td>
<td>0.202 - 5.073</td>
<td>0.989</td>
</tr>
</tbody>
</table>
Table 3 - there appears to be something wrong with the results for diabetes -
the odds CI is not symmetrical about the point estimate, and the P value is >1!

**Yes the p-value for diabetes was typo error and we corrected it and this should be 0.640 as shown in the latest Table 3.**

iii) Ethnicity reports a single OR - but this is a 3-category variable?

**Yes we agree that odds ratio for ethnicity should be three categories and we have now corrected it to 3-category and this is now presented in the latest Table 3.**

8. Table 3 - no need to state "The finding is significant..."

**We deleted the above phrase "The finding is significant..." from the Table 3.**

Discussion

9. First para - the statement "This fall within the range that had been reported in other studies", is followed immediately by "this is lower than secondary care and similar to one of the primary care study" - these statements are slightly at odds with one another; at any rate, it would be useful to provide references in the second sentence.

**We have now deleted "This fall within the range that had been reported in other studies". We have now separated the references and put them under references for secondary care and reference for primary care to read as**
The prevalence of resistant hypertension in this study is 8.8%. This is lower than that seen in secondary care [8, 30, 31] but is similar to a primary care study [18].

10. It would be helpful to explain why the adjusted OR appear to differ considerably from the unadjusted (e.g. for CKD, 2.8 vs. 1.6), as well as three factors becoming statistically significant. How about confounding?

In our study, the possibility of interaction between variables could be present as some of the variables (age and chronic kidney disease) which were not significant during the univariate analysis but became significant after multivariate logistic regression. However when we ran analysis to check for interaction between body mass index and chronic kidney disease, there was actually no interaction as the analysis produced a p value of 0.787 with 95% CI of 0.882-1.100 suggesting that there was no interaction.(please refer to paragraph 7 under discussion section).

11. re. the negative association with age, I wonder if this could be expanded upon?

*Under discussion paragraph 3, we have expanded the about the negative association with age to read as*

Our study sample is made up of older patients as seen from the mean age of 66.9 years. That resistant hypertension is negatively associated with age could be due to the survival effect of the older patients, whereby those with resistant hypertension have already succumbed to the complications of uncontrolled or resistant hypertension.

12. some discussion of drug types being used might be of interest.

*We have now expanded under the results section (paragraph immediately below Table 1) some details on control rates with use of 2 and 3 agents. We also added information on the*
use of diuretics, the percentage of patients on and not on diuretics. This will be useful as the definition of resistant hypertension includes a diuretic.

The average number of anti-hypertensive agents used was 2.0±1.0. The control rate of those on 2 drugs was 52.3% while it was 48.0% for those on 3 drugs. Three fifths (60.9%) of the diabetics and two fifths (41.3%) of the patients with CKD were on 3 antihypertensive agents. Calcium-channel blockers were the most commonly prescribed drug (53.2%) followed by angiotensin converting enzyme inhibitors or angiotensin receptor blockers (51.0%), beta-blockers (44.5%), Diuretics (32.5%) and alpha-blockers (3.5%). For those patients who were on at least three drugs, 70.2% (n=181) were on diuretics and 29.8% (n=77) were not on diuretics. Among those patients who were on at least 3-antihypertensive agents including diuretics, 42.5 %(n=77) achieved blood pressure target while 57.5% (n=104)had hypertension resistant. On the other hand, of those on at least 3 antihypertensive drugs which did not include a diuretic 96.1 %(n=74) were controlled and 3.9%(n=3) were not.

Consequently, under discussion paragraph 6, we have added some discussion in about number of drugs used as suggested by you to read as

Many studies have shown that most patients with hypertension need 2 or more drugs to achieve target BP [34-36]. Not surprisingly because the average number of antihypertensive drugs in our study was 2. We also found poor control rates amongst those on only 2 drugs, even those on 3 drugs had lower than 50% control rate. When control is not to target particularly when patients are already on 3 drugs, the recommendation is that one of the drugs should be a diuretic. However we found that overall the use of diuretics was low. Because the definition of resistant hypertension needs to include the use of a diuretic, perhaps our prevalence of resistant hypertension
may be higher if one of the drugs of those not controlled while on 3 drugs not including a diuretic was replaced with a diuretic.

Minor Essential Revisions

13. There are a number of grammatical errors throughout the manuscript; the authors may wish to seek help with this.

*We sought help for proof reading and hope the grammatical errors have been improved.*
Reply to the reviewer (Marianne E Gee)

Thank you very much for all your pertinent comments. I have made the revisions as below.

Major Compulsory Revisions

1. Sampling strategy. The authors state that the sample was randomly selected.

Please also describe:

a. How the participant were recruited (i.e., by their doctor, invitation letter, phone call, etc).

This sample was randomly selected from patients registered with our primary care clinic at a teaching hospital. Random numbers based on the patients’ registration number with the clinic was generated by computer. (Please refer to the data collection section)

This sample was selected randomly based on the registration number with the clinic generated by computer.

b. The number of patients that were eligible, the number that were selected and recruited, the number that agreed to participate and the overall response rate

The sample size was calculated using Epi Info 7.0, based on a prevalence of resistant hypertension of 5% [18]. The estimated sample size was 1283 based on the power of 90% and 95% CI with alpha value of 0.05. Since we did not have a database of patients with hypertension, in our clinic, when a randomly selected patient had hypertension, he or she was eligible and was entered into our sample. This was repeated till we reached the total sample size we needed. Hence all eligible patients who had been randomly selected were sampled and entered into our study; there was no response rate calculation done as all
eligible were selected to be in the study. In the end, a total of 1222 hypertensive patients were eligible for this study, out of this 1217 (99.6%) patients had complete drug therapy data and were entered into the analysis. If a response rate was needed this would be the response rate.

c. Did the authors compare the sample to the source patient population – were there any differences that would suggest selection bias?

_The number was randomly selected from the clinic, so it will represent the population in the clinic and there was no selection bias._

2. More clarity is need around data collection. In particular, please describe:

a. How information was extracted from the medical record.

_We now have described the extraction of information from the medical record under data collection section to read as_

All patient records were in paper form. We extracted the patients’ information based on the last entry in 2007 from their records manually according to a predetermined Performa (clinical report form) which included the patient’s socio demographic, blood pressure, weight, height, biochemical profile and use of anti-hypertensive agents. This was then entered into an Excel electronic format and then converted to an SPSS format for analysis using SPSS version 21.

as there more than one abstractor and were abstractors trained?

_Only one trained and very experienced abstractor did the data collection. The research assistant has been working in our research centre for more than 10-years. The accuracy of_
the data entry was subsequently checked by the investigators themselves and any error found was corrected accordingly.

We have now added all this into the manuscript under Data Collection

The data was captured by a trained and experienced abstractor and accuracy of data entry was checked by the investigators themselves.

Was the most recent medical record dating back from Dec 31, 2007 reviewed or all entries for 2007?

Yes. We took the most recent data dating back from Dec 31, 2007. (Please refer to the data collection section)

What was the span of time between Dec 31, 2007 and the date for the charts?

We choose the span of a six- month period as the usual follow up interval in our clinic was between 3 to 6 months.

b. Under ‘Data collection’, the authors indicate that sociodemographic data, weight and BP were captured from patient records. Please also indicate what source of information was used to capture height, to define presence of CKD, types of medications, and smoking.

All data was captured from patient record. We had included the information on height measurement, definition of presence of CKD, types of medications and smoking under data collection to read as

Height and weight were recorded using a stadiometer and digital weighing machine. Body mass index (BMI) was calculated as weight in kilograms per square meter (kg/m$^2$).
We used the Cockcroft-Gault estimated glomerular filtration rate formula to calculate the renal function. The presence of chronic kidney disease (CKD) was defined as estimated GFR < 60 ml/min. Anti-hypertensive drug use was also captured from medical records and classified into the following classes: renin-angiotensin-system (RAS) inhibitors encompassing angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB); beta-blockers (β-blockers), calcium-channel blocker (CCB), diuretics and alpha-blockers (α-blockers).

Resistant hypertension in this study is defined as office BP \( \geq 140 \) and/or 90 mmHg despite the use of at least three antihypertensive drugs, one of which is a diuretic. Diabetes mellitus (DM) was based on the doctors’ diagnosis or the use of hypoglycemic agents or both stated in the medical records. Smokers were defined as current if they were still smoking; non smokers as those who never smoked or currently not smoking regardless of when they had stopped smoking as indicated on the patient records.

c. The authors indicate that diabetes was determined by self-report or use of hypoglycemic drugs - does this mean that an interview was also administered? If yes, why was this done – couldn’t diagnosis of diabetes have been captured from the medical record? How was the interview administered and by whom? How much time was there between the interview and the chart date?

*Sorry for the mistake, the diagnosis was captured from the medical records based on the attending doctors’ diagnosis or the use of hypoglycemic agents. We have changed this under data collection to read as*

Diabetes mellitus (DM) was based on the doctors’ diagnosis or the use of hypoglycemic agents or both stated in the medical records.
d. How did the authors handle antihypertensive two-class combinations in the definition of resistant hypertension?

*Single pill or fixed drug combination are not available in our clinic and hence were not used at all. We counted each antihypertensive agent separately and, we defined those patients with hypertension resistant if they were on diuretics and at least two other antihypertensive agents and yet the blood pressure was $\geq 140/90$ mmHg for non-diabetics or $\geq 130/80$ mmHg for diabetics.*

3. Statistical revisions

a. Please provide confidence intervals for proportions, given that this is a sample of patients used to represent the underlying patient population

*The confidence interval for proportion were added in the result section, 4th paragraph to read as*

**Overall prevalence of resistant hypertension was 8.8% (N=107) with 95% CI 7.21 - 10.39.**

Miner Essential Revisions

1. In Table 1, please present the same measure of variability for systolic and diastolic blood pressure. For systolic, you have used interquartile range and for diastolic, standard deviation. If the distribution of systolic blood pressure is skewed, then present both the interquartile range and the SD for both systolic and diastolic.

*Our data showed the systolic BP was skewed and diastolic was normal distribution, so we used IQR and mean respectively. However we agree with you that it is better to standardize it and we have now amended both to IQR. The reading in the table now reads as*
17

Systolic blood pressure± interquartile range, mmHg  130±10

Diastolic blood pressure± interquartile range ,mmHg  80±10

2. In the logistic regression model (Table 3) please show the categories used for ethnicity – In table 1 the authors show 3 ethnicity groups, but in Table 3 only ‘ethnicity’ is listed suggesting that it has been included as a dichotomous variable. Which group is the referent category? Likewise, which gender is the referent category?

*Thank you very much for the suggestion as this will make the table much clearer. We have now added the 3 categories of ethnicity and Indians was the reference group. For the gender, male was the reference group. Now it will read as*

Table 3 Predictors of resistant hypertension at UMMC (N=1217)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR*</th>
<th>95% C.I.</th>
<th>P=value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2.89</td>
<td>1.562</td>
<td>5.345</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m2 increase)</td>
<td>1.05</td>
<td>0.994</td>
<td>1.102</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>0.96</td>
<td>0.928</td>
<td>0.988</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.88</td>
<td>0.511</td>
<td>1.511</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malays</td>
<td>1.30</td>
<td>0.638</td>
<td>2.633</td>
</tr>
<tr>
<td>Chinese</td>
<td>1.20</td>
<td>0.618</td>
<td>2.339</td>
</tr>
<tr>
<td>Indians</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.01</td>
<td>0.202</td>
<td>5.073</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1.33</td>
<td>0.729</td>
<td>2.417</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.57</td>
<td>0.903</td>
<td>2.744</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR: Odds Ratio, CI: Confidence Interval, * Adjusted odds ratio.** p-value is <0.05.

3. In Table 3, please indicate the unit of increase for BMI (I assume that it is per 1kg/m2 increase)

*Yes and we have now added the unit into the Table 3 above.*
4. Throughout the paper, the authors have used the term ‘cohort’ which implies that that a
group of people has been followed over time in a longitudinal study. It would be more
appropriate to call this a ‘sample’ instead, since it appears that the study is cross-sectional.

We used cohort as our original data base is actually a 10-year retrospective longitudinal
study. However, the data we present here is only based on the data in 2007 and therefore
appears as a cross sectional study. Thus we agree with you that for the purpose of this
analysis it is better to use “sample” instead of “cohort”. Hence we have changed the word
“cohort” to “sample”.

Discretionary Revisions

1. In Table 3, present odds ratios to 1 or 2 decimal places. It is unconventional to use 3
decimal places and suggests greater precision that your sample likely allows.

Thank you very much for the suggestion and we have now changed it to 2 decimal point as
shown in the Table 3 below.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR*</th>
<th>95% C.I.</th>
<th>P=value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2.89</td>
<td>1.562</td>
<td>5.345</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m2 increase)</td>
<td>1.05</td>
<td>0.994</td>
<td>1.102</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>0.96</td>
<td>0.928</td>
<td>0.988</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.88</td>
<td>0.511</td>
<td>1.511</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malays</td>
<td>1.30</td>
<td>0.638</td>
<td>2.633</td>
</tr>
<tr>
<td>Chinese</td>
<td>1.20</td>
<td>0.618</td>
<td>2.339</td>
</tr>
<tr>
<td>Indians</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.01</td>
<td>0.202</td>
<td>5.073</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1.33</td>
<td>0.729</td>
<td>2.417</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.57</td>
<td>0.903</td>
<td>2.744</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Discussion, paragraph 3 – please be more specific on the cohort effect where older patients succumb to complications, since there are many complications that would not bias the findings– do you mean specifically a survivor effect where older patients with uncontrolled high blood pressure have died?

Yes we mean that. We have now changed the sentence to

Our study sample is made up of older patients as seen from the mean age of 66.9 years. That resistant hypertension is negatively associated with age could be due to the survival effect of the older patients, whereby those with resistant hypertension have already succumbed to the complications of uncontrolled or resistant hypertension.

3. Strengths and limitations –paragraph 2 - please include a reference for the last sentence

We shifted the reference to the last sentence to read as

A limitation of our study is that adherence was not available from the patient records. If adherence is taken into account, the “true” resistant hypertension may be lower as many studies have shown that “resistant hypertension” is commonly due to non-adherence. However it is rather difficult for doctors to assess the adherence in primary care setting. Pill counting or use of electronic device is indicated to confirm the adherence, but this may not be practical in a real clinical setting [37-39].

Minor issues not for publication

1. Abstract under conclusion – should be ‘is present in nearly one in ten hypertensive patients…”

We amended the abstract under conclusion to be read as
Resistant hypertension is present in nearly one in ten hypertensive patients on treatment. Hypertensive patients who are having underlying chronic kidney disease are associated with higher odds of having resistant hypertension. Hence, in managing patient with hypertension, primary care physicians should be more alert and pay attention to those patients with chronic kidney disease as they are more likely to develop resistant hypertension. By doing that, these patients can be treated more aggressively earlier in order to achieve blood pressure target.

2. Define BP acronym at first use. This should be done in sentence one of the background.

_We define the BP acronym at first use in the background section, paragraph 1 to read as_

Resistant hypertension is an important medical condition as uncontrolled blood pressure (BP) is associated with a fourfold risk of cardiovascular events compared with hypertensive patients achieving BP targets [1, 2].

3. Discussion:

a. Paragraph 1, sentence 2 should be “falls” not “fall”

_We had actually deleted this sentence “This falls within the range that had been reported in other studies.” as another reviewer said that this sentences is rather confusion in the paragraph._

b. Paragraph 1, sentence 3 would read better as “This estimate is lower than the those previously observed in secondary care settings [provide references] and similar to estimates from primary care settings [provide references].”

_We amended as what you had suggested to read as_
The prevalence of resistant hypertension in this study is 8.8%. This is lower than that seen in secondary care [8, 30, 31] but is similar to a primary care study [18].

c. Paragraph 2, sentence 1 “findings” not “finding” and “had” not “was”

*We amended the sentence as what you had suggested to read as*

Our findings also show that hypertensive patients with CKD had 2.9 times the odds of having resistant hypertension compared to those without CKD.

d. Paragraph 2, sentence 2 “…increased sensitivity to salt resulting in sodium…”

*We amended the sentence as what you had suggested to read as*

One possible reason is that there is increased sensitivity to salt resulting in sodium and fluid retention in the patient with CKD [32].

e. Paragraph 3, sentence 1 “findings” not “finding”

*We had changed the word of “finding” to “findings” as what you had suggested, however we would like to pointed out that another reviewer suggested to add another two variables of dyslipidaemia and smoking into multivariate logistic regression and by doing so the findings, BMI is no more significant and we changed our sentence accordingly in paragraph 4 sentence 2 to read as.*

Our study has also shown obesity is not associated with resistant hypertension and this is not consistent with findings in other studies [3].

f. Para 3, sentence 2 “…shown that older age is associated…”

*We amended the sentence to read as*
Our study sample is made up of older patients as seen from the mean age of 66.9 years. That resistant hypertension is negatively associated with age could be due to the survival effect of the older patients, whereby those with resistant hypertension have already succumbed to the complications of uncontrolled or resistant hypertension.

g. Strengths and limitations, para 2, sentence 1 “…study is that adherence to medication was not available…”

We amended the sentence as what you had suggested to read as

A limitation of our study is that adherence to medication was not available from the patient records.

h. Conclusion – “The prevalence of resistant hypertension in this primary care population of people with hypertension is relatively low”

We amended the sentence as suggested to read as

The prevalence of resistant hypertension in this primary care population of people is relatively low.

i. Conclusion last sentence “…especially those who have CKD or who are obese”

We amended the sentence as suggested and we had removed “who are obese “as following the reanalysis the obesity is no more longer significant.

to read as

These results indicate the clinicians should recognize resistant hypertension earlier, especially those who have CKD so that early referral or intensifying in terms of treatment regimes can be in place.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

We sought help for proof reading and hope the grammatical errors have been improved.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests