PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multi-state Markov model application for blood pressure transition among the Chinese elderly population: A quantitative longitudinal study
AUTHORS	Zheng, Xujuan; Xiong, Juan; Zhang, Yiqin; Xu, Liping; Zhou, Lina; Zhao, Bin; Wang, Yuxin

VERSION 1 – REVIEW

REVIEWER	Almalki, Ziyad Prince Sattam bin Abdulaziz University, Clinical Pharmacy
REVIEW RETURNED	16-Jan-2022

GENERAL COMMENTS	This manuscript is titled " Multi-state Markov model application for blood pressure transition among Chinese elderly population: A longitudinal study" The authors examined the transitions between different blood pressure states in the Chinese senior population using a multi-state Markov model. Results showed that High blood pressure in old women and normal hypertension in elderly men increased knowledge of early prevention. Elderly persons should get at least one annual exam to avoid hypertension development. Age, BMI, and glucose were risk factors for hypertension progression from normal to increased. The computed transition probabilities and sojourn time may help health practitioners develop preventive approaches and focused treatments for Chinese elderly population. Overall, this is a well-written manuscript. However, the authors didn't make any contribution to the research literature in this area of investigation. Early prevention is recommended, and the studies' covariates are well documented in the literature that they are a significant driver of elevated BP. Finally, the elderly is at high risk of transition to hypertension compared to younger patients. Specific comments/inquiries are below: Page 5, line 45: The author didn't provide many details on the patients included in the study. Several factors were not taken under consideration, such as smoking, history of CV disease, or medical conditions. These and others are a considerable factor for BP elevations. Page 6, line 16: "of X hospital," Please specify the hospital. Page 10, line 23: In table 4, Please specify the reference group in the footnote, and also it is good to include the insignificant factors. Page 11, line 5:

	There are some statements that are already mentioned in the introduction. “Hypertension is regarded as the leading cause of cardiovascular and cerebrovascular diseases; and the most frequent risk factor for cardiovascular-related mortality, morbidity, disability and health expense in the global population [9-14]. In addition to hypertensive state, the elevated state is also identified as a higher risk of fatal cardiovascular disease. Thus, it is of significance to investigate the transition patterns among different levels of blood pressure, and the factors influencing the progression and regression of blood pressure for early detection and prevention [30].”

REVIEWER	xu, tingting Capital Medical University, school of publich health
REVIEW RETURNED	17-Feb-2022

GENERAL COMMENTS	Thank you so much for your inviting. In general, the topic of this manuscript is useful and interesting, but author should be careful for the discussion of the representativeness of study site. I have four comments for this study. - Please add more discussions on robustness of transition probabilities, and add sensitivity analysis of transition probabilities by subgroup of people. - If people with elevate state of blood pressure, would they received some preventions? Author should give descriptions. - Author showed the transition probabilities of one, two, three year, please supplement sample’s miss information of one, two, three years for different blood pressure state, and give corresponding discussion. - This manuscript needs careful editing by someone with expertise in technical English editing paying particular attention to English grammar, spelling, and sentence structure so that the goals and results of the study are clear to the reader.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Ziyad Almalki, Prince Sattam bin Abdulaziz University

Comments to the Author:

This manuscript is titled "Multi-state Markov model application for blood pressure transition among Chinese elderly population: A longitudinal study" The authors examined the transitions between different blood pressure states in the Chinese senior population using a multi-state Markov model. Results showed that High blood pressure in old women and normal hypertension in elderly men increased knowledge of early prevention. Elderly persons should get at least one annual exam to avoid hypertension development. Age, BMI, and glucose were risk factors for hypertension

progression from normal to increased. The computed transition probabilities and sojourn time may help health practitioners develop preventive approaches and focused treatments for Chinese elderly population.

Overall, this is a well-written manuscript. However, the authors didn't make any contribution to the research literature in this area of investigation. Early prevention is recommended, and the studies' covariates are well documented in the literature that they are a significant driver of elevated BP. Finally, the elderly is at high risk of transition to hypertension compared to younger patients.

Specific comments/inquiries are below:

- Page 5, line 45:

The author didn't provide many details on the patients included in the study. Several factors were not taken under consideration, such as smoking, history of CV disease, or medical conditions. These and others are a considerable factor for BP elevations.

Response: Thank you very much for your comments. The socio-demographic and clinical characteristics of these participants such as age, gender, marital status, blood pressure, glucose, BMI, and medical conditions including diabetes and abnormal ECG (indicating CV disease) were described in Table 2. However, the other significant covariates such as smoking and other medical conditions did not be included in the current study, which was added as one limitation of study in the revised manuscript. Thanks a lot.

The added contents were:

Some significant covariates, such as various lifestyle habits of diet, smoking, exercise, other medical conditions, and psychological status, were not covered in the current study, and are worthy of investigation in further research.

- Page 6, line 16:

"of X hospital," Please specify the hospital.

Response: The full name of hospital "the No.2 Affiliated Hospital of Xiamen Medical College" was added in the revised manuscript. Thanks a lot.

- Page 10, line 23:

In table 4, Please specify the reference group in the footnote, and also it is good to include the insignificant factors.

Response: The reference group in the footnote and the insignificant factors were added in Table 4 of the revised manuscript. Thanks a lot. The revised Table 4 was shown as followed:

Table 4 Covariate effects on blood pressure states transitions

Covariate	Normal–Elevated HR (95% CI)	Normal-Hypertensive HR (95% CI)	Elevated–Normal HR (95% CI)	Elevated – Hypertensive HR (95% CI)
Gender	1.131 (0.807, 1.586)	0.544 (0.288, 1.028)	0.606 (0.412, 0.891)	1.461 (0.999, 2.136)

BMI	1.038 (0.992, 1.086)	1.124 (1.058, 1.195)	1.017	(0.963,	1.019 (0.983, 1.057)	
			1.074)			
Age	1.016 (0.980, 1.054)	1.042 (1.010, 1.075)	1.018	(0.990,	1.017 (0.997, 1.037)	
			1.047)			
Glucose	1.013 (0.947, 1.083)	0.876 (0.697, 1.102)	0.827	(0.715,	1.054 (1.012, 1.097)	
			0.956)			
Marriage	0.989 (0.574, 1.702)	0.961 (0.347, 2.665)	1.073	(0.607,	0.866 (0.630, 1.189)	
			1.897)			
Abnormal ECG	0.737 (0.516, 1.052)	0.920 (0.479, 1.767)	0.794	(0.545,	1.026 (0.825, 1.275)	
			1.155)			

Reference categories of covariates: gender, ref=male; marriage, ref=single/divorced/widowed; abnormal ECG, ref=normal.

- Page 11, line 5:

There are some statements that are already mentioned in the introduction.

“Hypertension is regarded as the leading cause of cardiovascular and cerebrovascular diseases; and the most frequent risk factor for cardiovascular-related mortality, morbidity, disability and health expense in the global population [9-14]. In addition to hypertensive state, the elevated state is also identified as a higher risk of fatal cardiovascular disease. Thus, it is of significance to investigate the transition patterns among different levels of blood pressure, and the factors influencing the progression and regression of blood pressure for early detection and prevention [30].”

Response: Thank you very much for your comments. The above repetition statements in the discussion that already mentioned in the introduction were deleted in the revised manuscript. Thanks a lot.

Reviewer: 2

Prof. tingting xu, Capital Medical University

Comments to the Author:

Thank you so much for your inviting.

In general, the topic of this manuscript is useful and interesting, but author should be careful for the discussion of the representativeness of study site. I have four comments for this study.

- Please add more discussions on robustness of transition probabilities, and add sensitivity analysis of transition probabilities by subgroup of people.

Response: Thanks a lot. According to your wonderful advice, we conducted the sensitivity analyses of transition probabilities by subgroup of age. It was noted that the results of sensitivity analyses were well aligned with the our findings of covariate effects on blood pressure states transitions, which indicated the robustness of the transition probabilities results from the Markov model.

The added contents in the revised manuscript were shown below:

We further stratified the study individuals by gender and age group, and the transition probabilities in the 3rd year originating from the normal state or the elevated state at baseline are illustrated in Figure 4 and Figure 5, respectively. The detailed corresponding numerical values are described in Table S1 (see Supplementary material). As shown, both female and male participants with age ≧65 years were more likely to progress to hypertension whether starting from the normal state or the elevated state within the next 3 years, in comparison with the corresponding participants who were <65 years old.

Figure 4. Transition probabilities originating from the normal state in the 3rd year, stratified by gender and age group. Subfigures in the upper row from left to right illustrate the transition probabilities with 95% confidence intervals to the normal state, elevated state and hypertensive state for female participants; the subfigures in the lower row from left to right show transition probabilities for male participants to normal, elevated, and hypertensive state, respectively. N2N: normal state to normal state; N2E: normal state to elevated state; N2H: normal state to hypertensive state.

Figure 5. Transition probabilities originating from the elevated state in the 3rd year, stratified by gender and age group. Subfigures in the upper row from left to right illustrate the transition probabilities with 95% confidence intervals to the normal state, elevated state and hypertensive state for female participants; the subfigures in the lower row from left to right show transition probabilities for male participants to normal, elevated, and hypertensive state, respectively. E2N: normal state to normal state; E2E: elevated state to elevated state; E2H: elevated state to hypertensive state.

Table S1: The six possible blood pressure state transitions with the corresponding probabilities in the 3rd year, stratified by gender and age group

Gender	Group	States transition	Transition probability
Female	<65	N2N	0.2387 (0.1874, 0.2879)
Female	>=65	N2N	0.1909 (0.1358, 0.2486)
Male	<65	N2N	0.2481 (0.1888, 0.2966)
Male	>=65	N2N	0.1793 (0.1205, 0.2238)
Female	<65	N2E	0.3207 (0.2599, 0.3631)
Female	>=65	N2E	0.2769 (0.1964, 0.3303)
Male	<65	N2E	0.2584 (0.1962, 0.3136)
Male	>=65	N2E	0.2013 (0.1143, 0.2550)
Female	<65	N2H	0.4405 (0.3909, 0.5232)
Female	>=65	N2H	0.5322 (0.4640, 0.6438)
Male	<65	N2H	0.4935 (0.4251, 0.5965)
Male	>=65	N2H	0.6195 (0.5516, 0.7572)
Female	<65	E2N	0.1192 (0.0935, 0.1460)
Female	>=65	E2N	0.1040 (0.0778, 0.1338)
Male	<65	E2N	0.1647 (0.1283, 0.2004)
Male	>=65	E2N	0.1983 (0.1236, 0.2291)
Female	<65	E2E	0.3208 (0.2858, 0.3562)
Female	>=65	E2E	0.3159 (0.2739, 0.3539)
Male	<65	E2E	0.3422 (0.3004, 0.3819)
Male	>=65	E2E	0.2809 (0.1910, 0.3133)
Female	<65	E2H	0.5600 (0.5193, 0.6032)
Female	>=65	E2H	0.5801 (0.5395, 0.6308)
Male	<65	E2H	0.4931 (0.4491, 0.5497)
Male	>=65	E2H	0.5208 (0.4863, 0.6653)

N2N: normal state to normal state; N2E: normal state to elevated state; N2H: normal state to hypertensive state; E2N: normal state to normal state; E2E: elevated state to elevated state; E2H: elevated state to hypertensive state;

- If people with elevate state of blood pressure, would they received some preventions? Author should give descriptions.

Response: Thank you very much for your comment. The related contents were added in the revised manuscript as shown below:

In this study, if an elderly individual was diagnosed with elevated blood pressure, health professionals in the community health center provided a face-to-face health education session and sent text messages to the patient describing how to prevent hypertension through diet, exercise, daily blood pressure testing, etc.

- Author showed the transition probabilities of one, two, three year, please supplement sample's miss information of one, two, three years for different blood pressure state, and give corresponding discussion.

Response: Thank you very much for your advice. In this study, we fitted a multi-state Markov model to describe how an individual moves between a series of blood pressure states. Suppose an individual's movement on the discrete states 1 (normal state), 2 (elevated state), 3 (hypertensive state) is governed by transition intensities The transition probability matrix is given as:

Where is the transition probability that an individual in state at time will transit to state at time , which can be solved by the Kolmogorov forward equation:

In a time-homogeneous model, , and the explicit solution of each element in is:

And

For example, represents the probability of an individual staying in the normal state within 3 years; represents the probability of an individual progressing from the normal state to the hypertensive state within 3 years. The probability of transitions from hypertension to normotension state or to elevation state is set to zero, given the hypertension state is the absorbing state.

The proposed multi-state Markov model relies on the following assumptions: the future state **only depends on the current state, with no dependence on historical states; the transition intensities remain constant over time**. The full likelihood of the model is then the product of probabilities of transition between **observed states, over all individuals and their observations**. The likelihood is maximized and the model parameters were estimated by the Quasi-Newton optimization algorithm.

The miss information of each follow up visit is summarized in the table below:

	2nd visit	3rd visit	4th visit	5th visit	6th visit
Missing	644	488	331	192	129
Total N	1833	1311	902	617	289
Missing Percent (%)	35.13	26.62	18.06	10.47	7.04

Notice that the number of individuals in each following visit is decreasing. That is due to hypertensive state is the absorbing state. We excluded the records after the individual moved to hypertensive state (1833-1311=522 individual moved to hypertensive state at second visit).

We do have individuals missing certain schedule visit. However, based on the theory above, **our fitted multi-state Markov model are quite robust and stable regarding to the effect of missing data,** because it only depends on the current state, and the transition intensities remains constant until the next observed state.

- This manuscript needs careful editing by someone with expertise in technical English editing paying particular attention to English grammar, spelling, and sentence structure so that the goals and results of the study are clear to the reader.

Response: A thorough proofreading of the manuscript was conducted by a professional company of "International Science Editing" to correct any spelling, grammar errors, and sentence structure. Please see the track changes in the revised manuscript. Thank you very much.