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Hypotension and survival: diagnostic criteria in Russian and United States population

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Aim. Based on Russian and United States population studies, to determine the criterion for distinguishing between normal and low blood pressure (BP), which is the most significant for predicting all-cause mortality.

Material and methods. We used data from prospective Russian studies of 14730 men aged 19-82 years (9307 deaths per 342309 person-years of follow-up) and 6141 women aged 18-72 years (2101 deaths per 158727 person-years of follow-up), and two United States population studies: the First National Health and Nutrition Examination Survey (NHANES I) in conjunction with the NHANES I Epidemiologic Followup Study, and the Second National Health and Nutrition Examination Survey (NHANES II) in conjunction with the NHANES II Mortality Study. The total American cohort included only white subjects: 8618 men aged 25-75 years (3130 deaths per 121794 person-years of follow-up) and 11135 women 25-75 years (2465 deaths per 176676 person-years of follow-up). Primary examinations were carried out in 1971-1982, while the latest information on the subjects' survival status was obtained in 2017 (Russia) and 1992 (USA). Kaplan-Meier curves and Cox proportional hazards models were created; all-cause death was taken into account as an outcome.

Results. Survival analysis using Cox models, in which, in addition to BP levels, sex, age and risk factors were taken into account, showed that in persons with a pronounced BP decrease, survival is worse in comparison with those with normal BP. Mean dynamic BP, unfavorable for all-cause mortality, was below 70 and 68 mm Hg and 76 and 72 mm Hg in men and women in the Russian and US cohorts, respectively.

Conclusion. Not only hypertension, but also severe hypotension is associated with increased all-cause mortality compared to normal BP. Survival decrease is manifested in severe hypotension, subject to sex and adjustment for age and risk factors.

Keywords: hypotension, population study, prospective observation, survival, Cox regression.

Relationships and Activities. The work was carried out within the state assignment to the National Medical Research Center for Therapy and Preventive Medicine "Risk factors of NCDs, their significance for predicting the health of the population of different age groups in some regions of the Russian Federation. Assessment of the effect on morbidity and mortality (population study)". Registration number: AAAA-A20-120013090086-0.

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Hypotension (HoTN) is a condition, the main manifestation of which is an excessive blood pressure (BP) decrease. According to the International Classification of Diseases, Tenth Revision (ICD-10), an excessive BP decrease is considered to be more than 20% of the norm.

The problem of HoTN has received much less attention in comparison with hypertension (HTN), HoTN has always been “in the shadow of HTN” [1]. This is understandable, since HTN is one of the most widespread cardiovascular diseases and at the same time a significant risk factor (RF) for noncommunicable diseases [2], while the HoTN prevalence is much less [3]. However, there is evidence that the dependence of mortality on BP is not steadily increasing, but U-shaped (more precisely, J-shaped), i.e. at an excessively low BP, mortality is higher in comparison with its normal level [4, 5]. However, the severity of this effect is inferior to the increase in HTN-related mortality.

There is no single approach to HoTN diagnosis: some researchers took into account only the BP level; according to another point of view, in addition to BP values, clinical manifestations of insufficient blood supply should be taken into account with the separation of HoTN in physiological and pathological [6].

The BP values, which are regarded as diagnostically significant for HoTN, vary even more. Thus, some foreign researchers consider HoTN in men as systolic blood pressure (SBP) of 110 or diastolic blood pressure (DBP) of 60 mm Hg, as well as in women — SBP of 100 or DBP of 60 mm Hg, regardless of age [7]. In Russia, the most common classification proposed by N.S. Molchanov in the 60s of the XX century, people aged ⩽25 years with SBP <100 or DBP <60 mm Hg were attributed to HoTN, and those aged >25 years with SBP <105 or DBP <60 mm Hg, regardless of sex [6].

At one time, there were disputes regarding the BP thresholds, the excess of which is considered an HTN. These thresholds were determined after the accumulation of data from prospective studies that allowed to study the relationship between BP values and cardiovascular outcomes, including mortality [8].

In this study, we used a similar approach to determine the HoTN criteria, unfavorable for survival.

The aim was to determine, based on Russian and United States population studies, the criterion for distinguishing between normal and low BP, which is the most significant for predicting all-cause mortality

Material and methods

The work used data from Russian prospective studies performed at the National Medical Research Center for Therapy and Preventive Medicine [9] and 2 US population-based studies: the First National Health and Nutrition Examination Survey (NHANES I) together with NHANES I Epidemiologic Followup Study, as well as the Second National Health and Nutrition Examination Survey (NHANES II) together with NHANES II Mortality Study. The studies were carried out in accordance with the Declaration of Helsinki principles.

In this work, we used data from a Russian cohort of 14730 men aged 19-82 years (9307 deaths per 342309 person-years of follow-up) and 6141 women aged 18-72 years (2101 deaths per 158727 person-years of follow-up).

For comparison, we used data from the combined American cohort (only white people): 8618 men aged 25-75 years (3130 deaths per 121794 person-years of follow-up) and 11135 women aged 25-75 years (2465 deaths per 176676 person-years of follow-up).

Primary examinations were carried out in 1971-1982, while the latest data on participants was obtained in 2017 (Russia) and 1992 (USA).

We analyzed age, sex, smoking status, total cholesterol (TC), SBP, DBP, heart rate (HR), body mass index (BMI). According to SBP and DBP values using the Hickam formula, the average dynamic BP (ADBP) was calculated.

For survival analysis, Kaplan-Meier curves [10] and Cox proportional hazards model [11] were created. All-cause death was taken into account as an outcome.

By creating Kaplan-Meier curves, survival was compared in hypo-, normo-, and hypertensive patients. To differentiate hypo- and normotensive persons, several criteria were used [6, 7, 12]; for each criterion, a separate analysis was performed. The criteria of Molchanov N.S. (1962) [6] and Pemberton J (1989) [7] are described in the introduction; according to Chefranova Zh. Yu. (2008) criterion [12], persons aged <35 years with SBP/DBP not higher than 100/60 mm Hg, those aged 36-54 years with SBP/DBP of no more than 110/70 mm Hg, and those aged >54 years with SBP/DBP of no more than 120/70 mm Hg were classified as HoTN. In all cases, HTN included persons with SBP and/or DBP more than or equal to 140 and/or 90 mm Hg.

To develop an original criterion for HoTN, several computational experiments was carried out studying 8 types of thresholds between groups of people with HoTN and normal BP based on ADBP: 68, 70, 72, 74, 76, 78, 80, 82 mm Hg (types I, II, III, IV, V, VI, VII, VIII, respectively). The lower ADBP limit in persons with normal BP was determined in accordance with one of above types, while the upper limit was 100 mm Hg; in persons with high normal

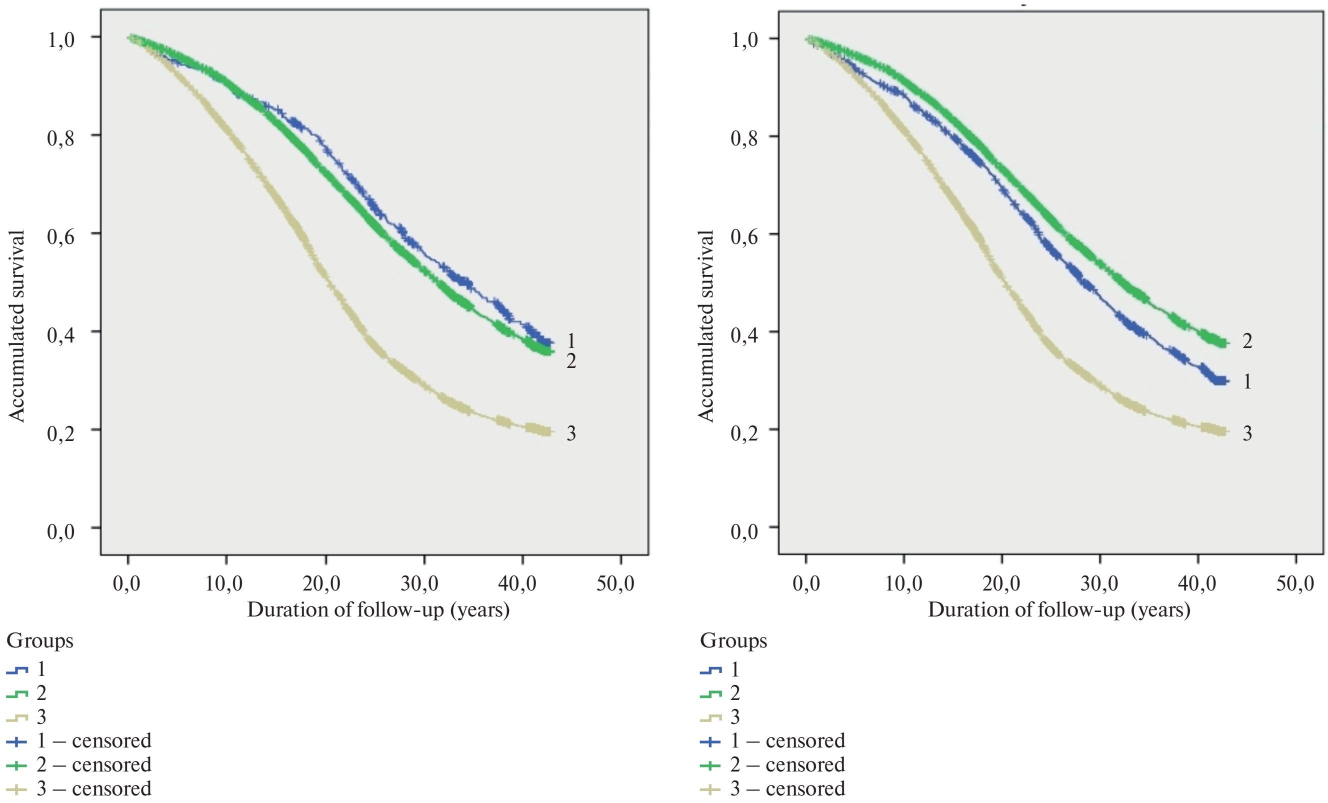

Figure 1. Kaplan-Meier curves in Russian men according to two HoTN criteria: on the left — Molchanov N.S. (1962) [6]; on the right — Chefranova Zh. Yu. (2008) [12].
Groups: 1 — hypertensive patients, 2 — normotensive people, 3 — hypertensive patients.

BP, the boundaries of ADBP were 100-106,7 mm Hg. To differentiate the HTN grades, we used ADBP values, equivalent to the corresponding SBP and DBP values [13]: the group of patients with grade 1-2 HTN included persons with ADBP 106,7-133,3 mm Hg, while grade 3 HTN consisted of those with ADBP >133,3 mm Hg. Cox proportional hazards models were created with independent variables including age, smoking status, HR, BMI, TC, and a categorical variable characterizing the level of ADBP. This variable had values from 1 to 5, which coded belonging to the group of people with HoTN, normal BP, high normal BP, grade 1-2 HTN, grade 3 HTN, respectively. Cox models were created for each of the eight threshold types separately for men and women, for the Russian cohort and the combined cohort from the US population. The models had the same independent variables (see above) and differed in regression coefficient values.

Results

The study of survival in HoTN persons in comparison with normo- and hypertension showed that the results differ significantly depending on the chosen criterion for HoTN [6, 7, 12]. In some cases, the survival curve for HoTN is higher in comparison with normotension, while according to some criteria, the ratio is reversed. Figure 1 shows as examples the survival curves for Russian men using Molchanov N.S. (1962) [6] and Chefranova Zh. Yu. (2008) [12] criterions, which demonstrated the above differences. For all of the above criteria, the differences in survival in persons with hypo- and normotension were relatively small.

The next step was to study survival in individuals with different BP, taking into account sex, age, and RFs. In this work, this was implemented by constructing Cox proportional hazards models separately for men and women. We used independent variables included age, smoking status, TC, BMI and HR values at the initial examination, as well as a categorical variable characterizing belonging to groups of HoTN, normal BP, high normal BP, grade 1-2 HTN, grade 3 HTN. Survival curves were created separately for each of the 5 values of above categorical variable.

We revealed a clear pattern — the lower the borderline ADBP between hypo- and normotension,

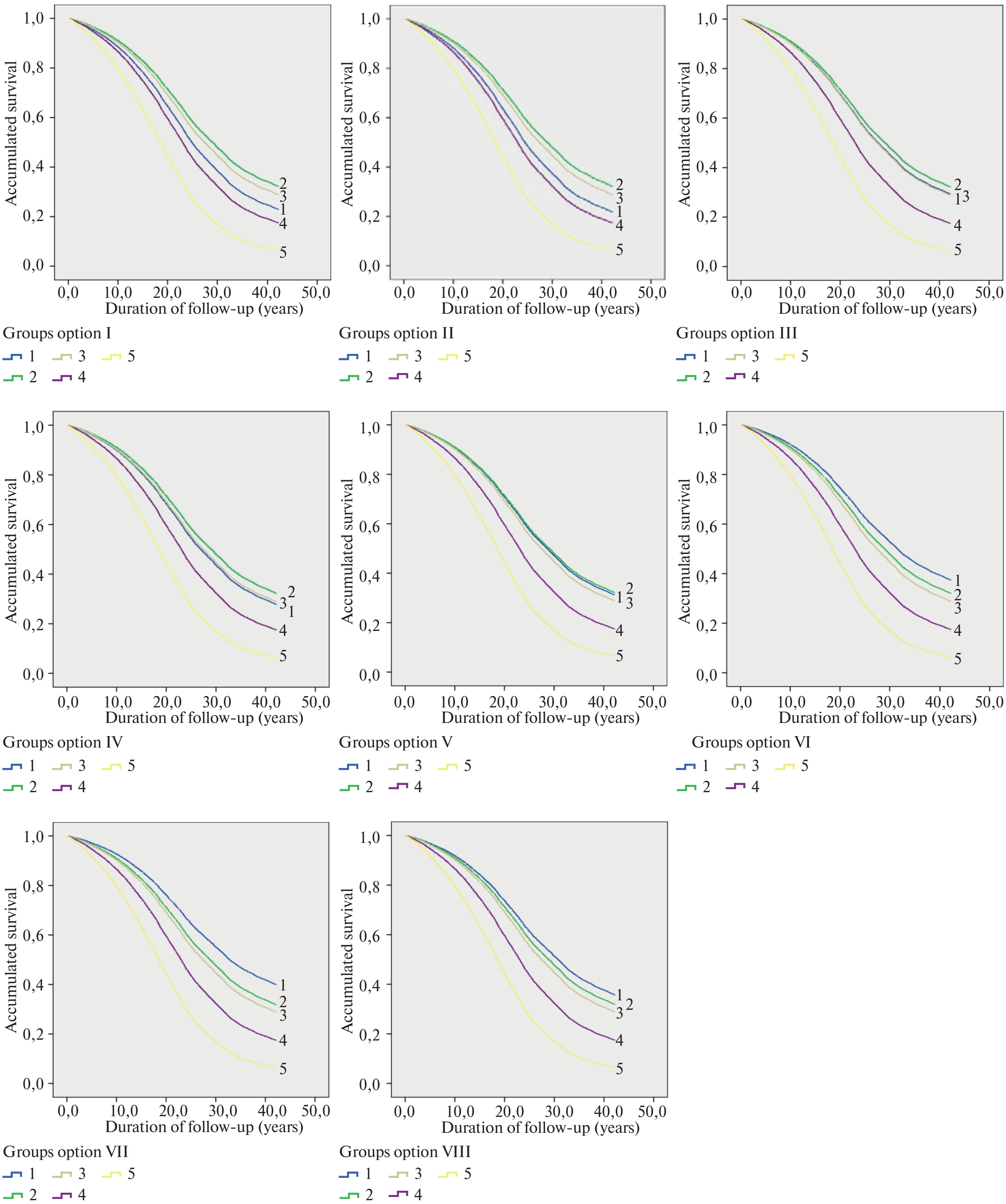

Figure 2. Survival curves estimated using Cox models in Russian men. The models adjusted for age, smoking status, HR, BMI, TC, as well as a categorical variable characterizing belonging to the hypo-, normo- or hypertension groups.
Groups: 1 — HoTN (one of the types I-VIII, the ADBP is less than 68, 70, 72, 74, 76, 78, 80 or 82 mm Hg), 2 — normal BP, 3 — high normal BP, 4 — grade 1-2 HTN, 5 — grade 3 HTN.

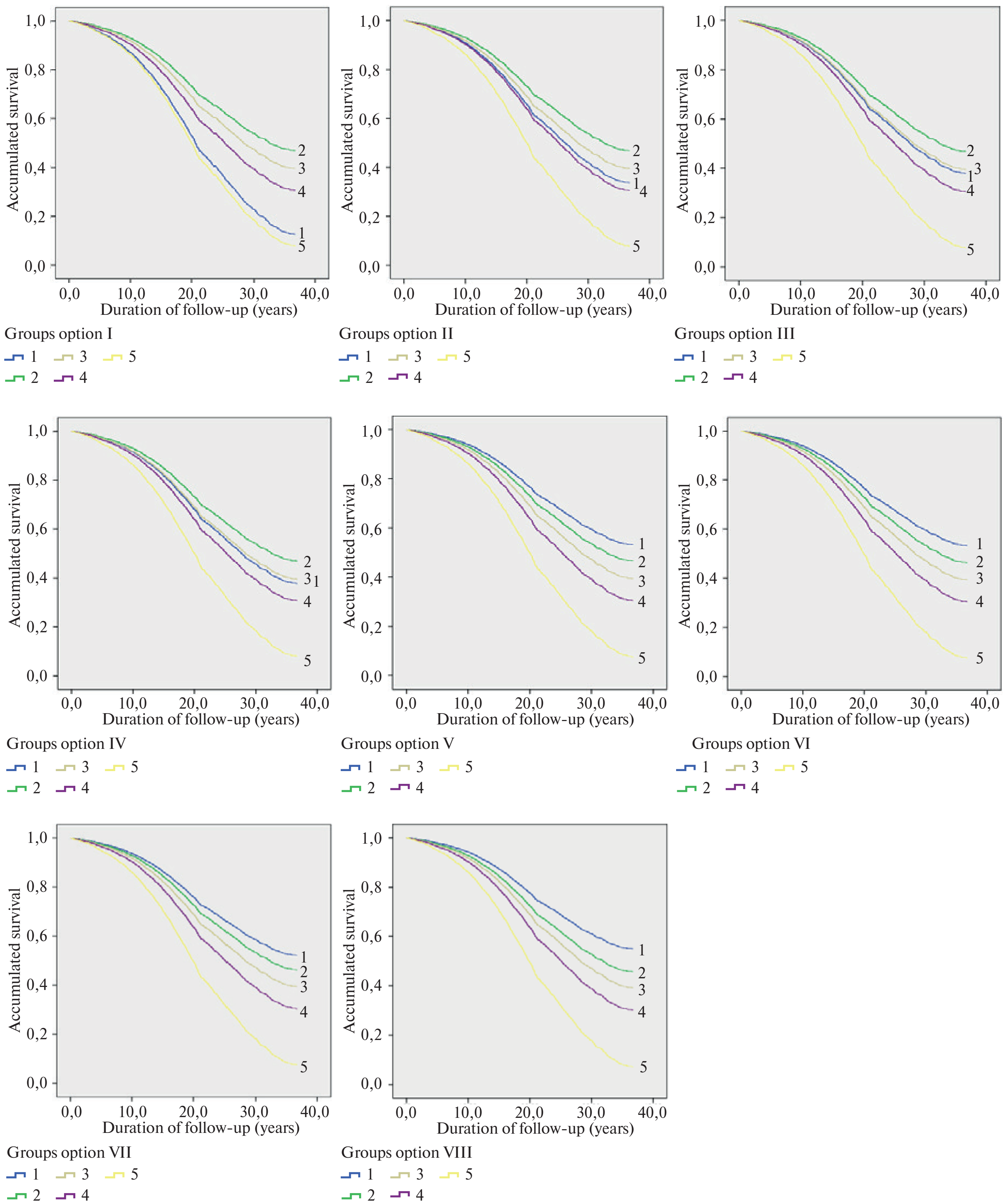

Figure 3. Survival curves estimated using Cox models in Russian women. The models adjusted for age, smoking status, HR, BMI, TC, as well as a categorical variable characterizing belonging to the hypo-, normo- or hypertension groups.
Groups: 1 — HoTN (one of the types I-VIII, the ADBP is less than 68, 70, 72, 74, 76, 78, 80 or 82 mm Hg), 2 — normal BP, 3 — high normal BP, 4 — grade 1-2 HTN, 5 — grade 3 HTN.

the worse the survival of hypotensive patients in comparison with normotensive ones. In each studied cohort, for men and women, the ADBP values were determined, which as a HoTN criterion, shows the worst survival in comparison with normotensive patients.

For example, Figure 2 shows survival curves estimated using Cox models in Russian men for above types of thresholds (I-VIII).

Figure 2 shows that for Russian men, the most unfavorable HoTN is with an ADBP of 70 mm Hg. With the shift of HoTN border to higher ADBP values, the survival curves of hypotensive and normotensive patients converge. Starting with type VI, the survival rate in hypotensive patients becomes better than in normotensive ones.

Figure 3 presents the results for Russian women, which demonstrates that they have the most unfavorable HoTN with an ADBP of 68 mm Hg (type I). As in men, as the threshold of ADBP increases, survival rate in HoTN compared to normotensive patients improves.

Similar computational experiments were carried out in the US cohort. The patterns are the same, but there are only quantitative differences. The thresholds of unfavorable HoTN were 76 and 72 mm Hg in men and women, respectively.

According to Cox models, differences in survival rate between unfavorable HoTN and normotension in the Russian and American cohorts using unweighted values do not formally reach significance due to the small cohort of hypotensive patients (Russian cohort, 24 men and 25 women; US cohort, 78 and 108, respectively). Similar Cox models were created after weighing with a single scaling factor of 10, while the differences between the selected HoTN types with normotensive people in all the cases described above become significant ($p<0,02$ or less).

Discussion

The HoTN criteria described in the literature in most cases were developed based on the clinical studies without prospective follow-up; the authors focused mainly on the clinical manifestations of inadequate blood supply to organs [6, 7, 12].

There are much fewer publications on the HoTN effect on survival rate and related conclusions are contradictory.

So, according to Robbins JM, et al. (1982) [14], low BP was associated with a decrease in cardiovascular mortality, and therefore HoTN was defined as a non-disease. The prospective study of Leiden (Netherlands) residents after adjustment for sex, age and basic health parameters showed no significant increase in the relative risk of all-cause death in people with low SBP or DBP [4]. According to Lapin V.V. (2008), the incidence of cardiovascular events in persons with stable HoTN does not differ from people with normal BP [15].

On the other hand, the prospective study of 1,5 thousand residents of Ohasama (Japan) aged 40 years and older with a follow-up of 6 years demonstrated an increased death risk not only with an increase, but also with a decrease in BP <119/64 mm Hg [5]. The latest large-scale studies of antihypertensive drugs have shown that SBP <120 mm Hg or DBP <70 mm Hg are associated with an increased risk of cardiovascular events and death [16]. The Russian cohort study of people aged 55 years and older adjusted for RFs revealed an association of cardiovascular mortality with both high BP and SBP <120 mm Hg [17].

The BP values, diagnostically relevant for HoTN, proposed by different researchers vary greatly. For example, the meta-analysis of papers for 1914-1955 considered the HoTN thresholds of SBP from 90 to 120 mm Hg and DBP from 40 to 70 mm Hg [6].

As a theoretical rationale for HoTN threshold, a BP value is proposed, which ensures the maintenance of cerebral flow autoregulation, which is about 70 mm Hg for SBP or 90/60 mm Hg for SBP/DBP [15].

Possible mechanisms of the negative effect of HoTN on survival rate are considered impaired cerebral circulation and autoregulation, neurohumoral dysregulation of BP, and the development of vascular (hypotonic) encephalopathy [18].

Thus, the question of the specific BP value, which distinguishes normo- and hypotension, negatively associated with survival, remains unclear.

We carried out the above computational experiments, using the ADBP values from 68 to 82 mm Hg as the boundary between normo- and hypotension with a step of 2 mm Hg. It turned out that, with adjustment for sex, age, smoking status, heart rate, BMI, TC, there is a range of low BP values associated with a deterioration in survival compared with normotensive patients. In the Russian population, with a 40-year follow-up, the survival rate is worse in men and women with an ADBP of 70 and 68 mm Hg, respectively. These observations were confirmed in the US population with a 20-year follow-up, where decrease in survival rate was observed in men and women with ADBP <76 and 72 mm Hg, respectively.

Identical patterns obtained from the three cohorts from populations of two different countries demonstrates the non-randomness of data obtained.

Study limitations. The problem of HoTN was actively studied in the first third of the 20th century. Then there was a renewed interest due to a sharp increase in its prevalence due to World War II. Due to the small number of modern publications, there are deviations from the journal requirements — some of the papers were published more than 10 years ago.

Conclusion

1. The relationship between BP and survival is not linear. Not only hypertension, but also severe HoTN are associated with an increase in all-cause mortality in comparison with normal BP.

2. The more stringent the HoTN criterion is used (the lower the threshold between hypo- and normotensiion), the worse the survival of hypotensive patients in comparison with normotensive ones.

3. Survival decrease is manifested only in case of severe hypotension — according to the 40-year prospective follow-up in the Russian population, an ADBP of 70 and 68 mm Hg in men and women, respectively.

4. The patterns were confirmed by 20-year prospective follow-up of the US population with an ADBP of 76 and mm Hg in men and women, respectively.

5. These patterns are manifested only with adjustment for sex, age and RFs, in particular, smoking status, HR, BMI, and TC.

Acknowledgments. The authors are grateful to all participants of the ESSE-RF study. This work was made possible by the free access to data from the NHANES series provided by the National Center for Health Statistics (NCHS), USA. Responsibility for the results of analysis, interpretation and conclusion lies with the article authors, while responsibility of NCHS is limited to primary data.

Relationships and Activities. The work was carried out within the state assignment to the National Medical Research Center for Therapy and Preventive Medicine "Risk factors of NCDs, their significance for predicting the health of the population of different age groups in some regions of the Russian Federation. Assessment of the effect on morbidity and mortality (population study)". Registration number: AAAA-A20-120013090086-0.

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