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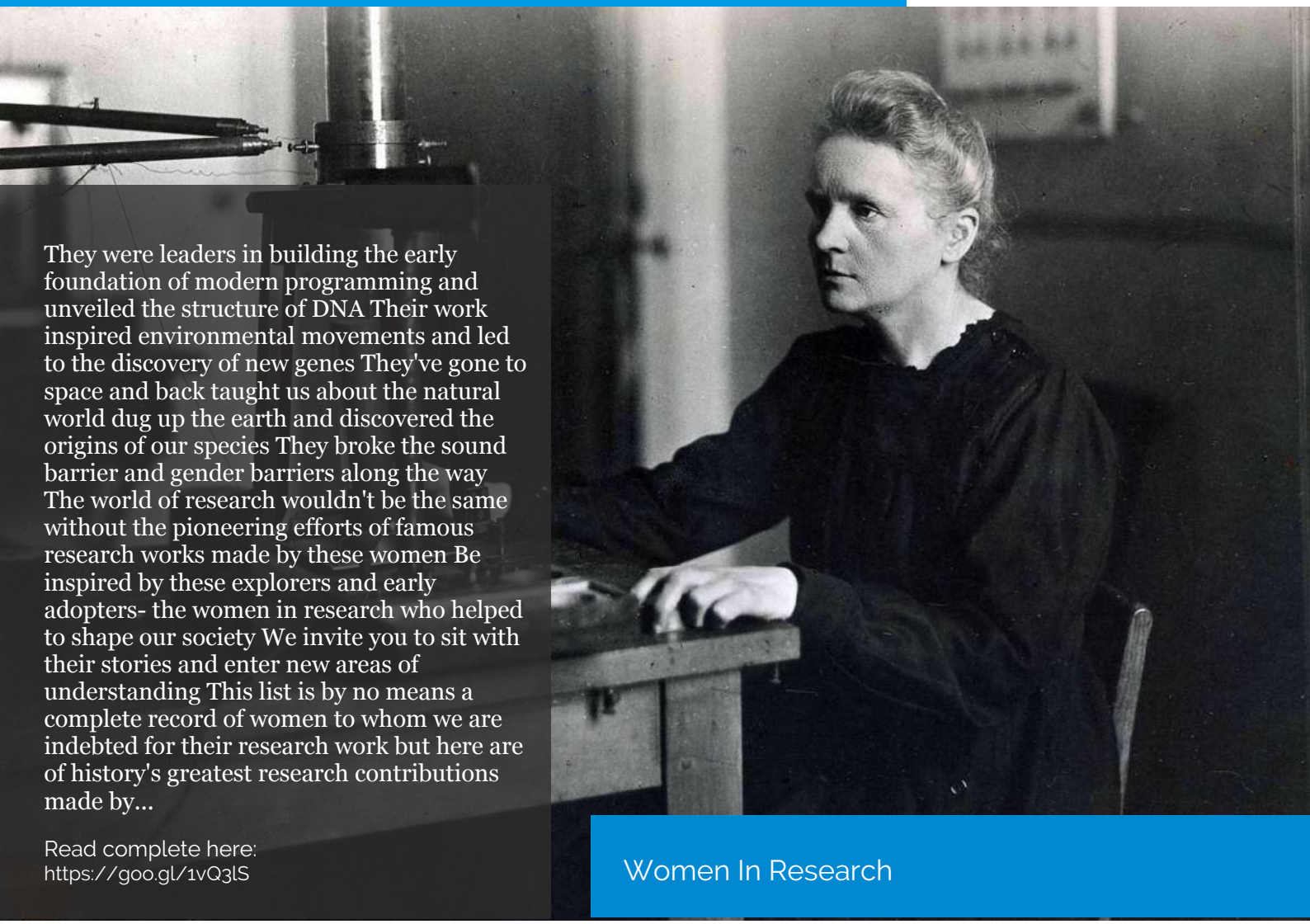

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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New Markers of Coronary Heart Disease with Old Myocardial Infarction: Certain Variants of Relative Length of Telomeric Repeats

Margarita A. Sazonova, Natalya A. Doroschuk, Marina D. Sazonova, Anastasia I. Ryzhkova, Mikhail A. Popov, Vasily N. Sukhorukov, Tatiana I. Kovyanova, Irina A. Starodubtseva, Dmitry F. Beloyartsev, Alexey V. Churov, Paolo Poggio, Donato Moschetta, Vasily P. Karagodin, Anton Yu. Postnov & Alexander N. Orekhov

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ABSTRACT

One of the possible factors in the occurrence of coronary heart disease with myocardial infarction is oxidative stress. Oxidative stress intensifies the formation of free radicals, causing defects in proteins and nucleic acids. This can lead to their partial or complete destruction. For example, the result of such destruction of DNA molecules may be a decrease in the length of telomeric repeats in the chromosomes of cells in coronary heart disease.

Therefore, the aim of this work was to analyze the association of certain variants of the relative length of telomeric repeats (VRLTR) with coronary heart disease with old myocardial infarction (CHD with MI).

Keywords: relative length of telomeric repeats; coronary heart disease with myocardial infarction; percentage of the calibrator; oxidative stress; protective effect; chromosomes.

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New Markers of Coronary Heart Disease with Old Myocardial Infarction: Certain Variants of Relative Length of Telomeric Repeats

Margarita A. Sazonova[α], Natalya A. Doroschuk[σ], Marina D. Sazonova[ρ], Anastasia I. Ryzhkova[ↀ], Mikhail A. Popov[¥], Vasily N. Sukhorukov[§], Tatiana I. Kovyanova[χ], Irina A. Starodubtseva[ν], Dmitry F. Beloyartsev[Θ], Alexey V. Churov[ζ], Paolo Poggio[£], Donato Moschetta[€], Vasily P. Karagodin[₣], Anton Yu. Postnov[₴] & Alexander N. Orekhov[₲]

ABSTRACT

One of the possible factors in the occurrence of coronary heart disease with myocardial infarction is oxidative stress. Oxidative stress intensifies the formation of free radicals, causing defects in proteins and nucleic acids. This can lead to their partial or complete destruction. For example, the result of such destruction of DNA molecules may be a decrease in the length of telomeric repeats in the chromosomes of cells in coronary heart disease.

Therefore, the aim of this work was to analyze the association of certain variants of the relative length of telomeric repeats (VRLTR) with coronary heart disease with old myocardial infarction (CHD with MI).

To measure the length of telomeric repeats, whole blood was collected, with the following DNA isolation from nuclear cells. The relative length of telomeric repeats was calculated based on the formula "2 to the power (-ΔCt)", where ΔCt = Ct of telomeres-Ct of albumin. In this case, Ct of telomeres is the threshold cycle of the telomeric repeat, and Ct of albumin is the threshold cycle of the albumin gene. The results of the relative length of telomeric repeats are presented as a percentage of the calibrator. DNA isolated from HeLa cell line was used as a calibrator.

By measuring variants of the relative length of telomeric repeats in the studied samples, an association of coronary heart disease with myocardial infarction with VRLTR-46, VRLTR-49, VRLTR-51, VRLTR-53 and VRLTR-56 was detected. At the same time, 6 of 21 variants of the relative length of telomeric repeats (VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71 and VRLTR-73) had a protective effect in coronary heart disease with myocardial infarction.

Therefore, in the present research work, we propose new markers of coronary heart disease with old myocardial infarction: certain variants of relative length of telomeric repeats.

Keywords: relative length of telomeric repeats; coronary heart disease with myocardial infarction; percentage of the calibrator; oxidative stress; protective effect; chromosomes.

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I. INTRODUCTION

One of the possible factors in the occurrence of coronary heart disease with myocardial infarction is oxidative stress [1-5]. Oxidative stress intensifies the formation of free radicals, causing defects in proteins and nucleic acids [6-10]. This can lead to their partial or complete destruction [11-15]. For example, the result of such destruction of DNA molecules may be a decrease in the length of telomeric repeats in the chromosomes of cells in coronary heart disease [16-20].

However, to date, there is no reliable data confirming the association of certain variants of telomeric repeat lengths with coronary heart disease with old myocardial infarction.

Telomeres are regions of chromosomal ends which contain tandem six-nucleotide repeats (TTAGGG) [21-25]. It is believed that they are intended for stable cell replication [26-30]. With each subsequent cell mitosis, the size of telomeric repeats decreases. Evidence has been obtained that a critical decrease in telomere size can cause degenerative changes in the cell followed by apoptosis [31-35].

It has been noted that individuals who have very short telomeres have a higher risk of developing coronary heart disease [35-40]. Scientists from Scotland have shown that individuals with shortened telomeres have a threefold increased risk of death over the next decade [41]. Short telomeric repeat lengths have been found in elderly patients with cardiomyopathy [42]. Type 2 diabetes mellitus has been found to be significantly increased in individuals with short telomeres compared to individuals with long telomeres [43].

Meanwhile, it was found that the speed of decrease in the length of telomeric repeats is almost the same for different types of cells and tissues. Therefore, the use of human blood leukocytes, as the most accessible biological material for research, seems to be optimal [42, 43].

So, the main direction in the study of telomeres turned out to be the detection of the association between certain variants of shortened telomeres and certain human diseases. For this reason, it seems to be appropriate to include the analysis of telomeric repeat length variants into the biomarkers studied in coronary heart disease with myocardial infarction.

II. MATERIALS AND METHODS

To measure the length of telomeric repeats, whole blood was collected, with the following DNA isolation from nuclear cells. The DNA extraction kit "DNA-Extran1" (CJSC Synthol, Russia) was used. The length of telomeric repeats was determined by quantitative real- time polymerase chain reaction (RT-PCR) using a BIO-RADCFX 96 Real-Time System amplifier (Singapore). The study of each sample was repeated three times.

The relative length of telomeric repeats was calculated based on the formula "2 to the power (-ΔCt)", where ΔCt = Ct of telomeres-Ct of albumin. In this case, Ct of telomeres is the threshold cycle of the telomeric repeat, and Ct of albumin is the threshold cycle of the albumin gene. It should be noted that the albumin gene acted as an internal control against which the length of telomeric repeats was determined. The results of the relative length of telomeric repeats are presented as a percentage of the calibrator. DNA isolated from HeLa cell line was used as a calibrator.

Since there were no significant age differences between the samples of patients with coronary

heart disease who had suffered a myocardial infarction and conditionally healthy study participants, normalization of the length of telomeric repeats by age was not performed.

Statistical analysis of the relative length of telomeric repeats was carried out using the IBM SPSS Statistics 27.0 software package.

III. RESULTS AND DISCUSSION

In 300 DNA samples from samples of patients with coronary heart disease with old myocardial infarction (CHD with MI) and conditionally healthy study participants, variants of the relative length of telomeric repeats (RTL) were analyzed using real-time PCR.

Methods of clinical examination, high-resolution B-mode ultrasonography and DNA extraction were used. The criteria for inclusion in the sample of patients CHD with MI were-

1. Men and women aged 45 to 79 years.
2. Old myocardial infarction in the anamnesis.
3. Pathological Q waves with or without symptoms in the absence of non-ischemic causes. 4. Lack of exclusion criteria.
4. Voluntary consent to participate in the study.

The criteria for excluding patients CHD with MI were:

1. Age younger than 45 or older than 79 years.
2. Abnormal anatomical configuration of the neck and muscles; pronounced tortuosity and/or depth of the carotid arteries, and/or unusual locations of arterial branches.
3. Presence of oncological and other chronic diseases requiring regular drug therapy, except arterial hypertension.
4. Congestive heart failure (NYHA class III-IV).
5. Refusal to sign informed consent to participate in the study.

Based on clinical examination and ultrasonography data.

Two samples will be created consisting of-

1. 150 patients with coronary heart disease with old myocardial infarction;
2. 150 conditionally healthy study participants. An analysis of the average value of variants of relative length of telomeric repeats (VRLTR) in the blood leukocytes of study participants was carried out (Table 1). In Table 1, the results are presented as the mean value of the VRLTR and the standard error to the mean. According to the results presented in Table 1, the average value of VRLTR is significantly lower in patients with coronary heart disease with old myocardial infarction compared to conditionally healthy study participants (by 25.0%).

Analysis of variants in the relative length of telomeric repeats in samples of patients with CHD with MI and conditionally healthy study participants was carried out using nonparametric statistics using the Wilcoxon rank test (Table 2) with further correlation analysis of mutations detected using the Wilcoxon test (Table 3). It should be noted that VRLTR have designations depending on their relative length in percents to the calibrator. The range of values for variants of the relative length of telomeric repeats in the studied samples ranged from 31% to 80%, in relation to the calibrator.

Table 1: Analysis of the Average Value of Variants of the Relative Length of Telomeric Repeats in the Blood Leukocytes of Study Participants

Samples of Study Participants	Mean Relative Length of Telomeric Repeats	Standard Error to the mean	Reliability of Results
Patients with coronary heart disease with old myocardial infarction	51	1.1	$p \leq 0.001$
Conditionally healthy study participants	68	1.4	$p \leq 0.05$

Table 2: Analysis of Variants of the Relative Length of Telomeric Repeats in Samples of Patients with Coronary Heart Disease with Old Myocardial Infarction (CHD With MI) and Conditionally Healthy Study Participants using the Wilcoxon Rank Test

Variants of the Relative Length of Telomeric Repeats	Type of Rank	Number of Ranks	Mean Rank	Sum rank
VRLTR -31	Negative	2	3.11	3.18
	Positive	2	1.27	1.65
	Neutral	3		
VRLTR -32	Negative	1	3.15	4.17
	Positive	2	2.56	4.58
	Neutral	4		
VRLTR -33	Negative	2	2.16	3.18
	Positive	2	2.05	3.16
	Neutral	3		
VRLTR -34	Negative	2	1.43	1.72
	Positive	1	2.26	2.26
	Neutral	4		
VRLTR -35	Negative	2	2.04	2.17
	Positive	2	1.12	1.21
	Neutral	3		
VRLTR-36	Negative	2	2.08	3.06
	Positive	3	3.14	4.08
	Neutral	2		
VRLTR-37	Negative	2	2.02	3.27
	Positive	2	3.02	4.09
	Neutral	3		
VRLTR-38	Negative	2	2.16	2.48
	Positive	3	2.29	2.87
	Neutral	2		
VRLTR-39	Negative	2	3.05	4.21
	Positive	1	4.83	4.83

	Neutral	4		
VRLTR-40	Negative	2	2.30	3.11*
	Positive	4	1.51	6.41*
	Neutral	1		
VRLTR-41	Negative	1	4.22	4.22*
	Positive	2	3.78	8.63*
	Neutral	3		
VRLTR-42	Negative	2	4.18	6.03
	Positive	2	3.05	4.97
	Neutral	3		
VRLTR-43	Negative	2	2.75	3.18*
	Positive	4	3.21	6.69*
	Neutral	1		
VRLTR-44	Negative	1	2.19	2.19*
	Positive	2	2.87	4.81*
	Neutral	4		
VRLTR-45	Negative	3	2.11	3.94
	Positive	1	3.16	3.16
	Neutral	3		
VRLTR-46	Negative	2	3.17*	7.30*
	Positive	4	5.32*	21.33*
	Neutral	1		
VRLTR-47	Negative	1	3.98	3.98*
	Positive	2	4.01	8.04*
	Neutral	3		
VRLTR-48	Negative	3	5.35	6.24
	Positive	2	4.14	6.45
	Neutral	2		
VRLTR-49	Negative	2	1.10*	2.24*
	Positive	4	2.21*	8.96*

	Neutral	1		
VRLTR-50	Negative	4	3.11	5.03
	Positive	2	2.15	3.15
	Neutral	1		
VRLTR-51	Negative	2	2.08*	6.18*
	Positive	4	6.16*	12.36*
	Neutral	1		
VRLTR-52	Negative	2	3.25	3.98
	Positive	1	4.08	4.08
	Neutral	4		
VRLTR-53	Negative	2	2.60*	7.84*
	Positive	3	5.45*	16.75*
	Neutral	2		
VRLTR-54	Negative	4	6.71	7.56
	Positive	1	4.12	4.12
	Neutral	2		
VRLTR-55	Negative	2	1.50	2.11
	Positive	2	2.15	2.94
	Neutral	3		
VRLTR-56	Negative	2	2.50*	5.09*
	Positive	4	5.04*	20.24*
	Neutral	1		
VRLTR-57	Negative	3	3.64	4.14
	Positive	3	5.16	6.12
	Neutral	1		
VRLTR-58	Negative	3	5.16	6.28
	Positive	2	3.11	3.54
	Neutral	3		
VRLTR-59	Negative	4	2.28*	5.56
	Positive	2	1.14*	4.27

	Neutral	1		
VRLTR-60	Negative	3	3.16	4.12
	Positive	2	5.41	5.98
	Neutral	1		
VRLTR-61	Negative	2	1.14	1.50*
	Positive	3	2.01	3.00*
	Neutral	2		
VRLTR-62	Negative	2	3.33	4.51
	Positive	2	2.50	3.57
	Neutral	3		
VRLTR-63	Negative	4	5.08*	20.46*
	Positive	2	2.24*	5.11*
	Neutral	1		
VRLTR-64	Negative	2	2.19	3.74
	Positive	2	3.11	4.26
	Neutral	3		
VRLTR-65	Negative	4	4.06*	16.28*
	Positive	2	2.02*	4.11*
	Neutral	1		
VRLTR-66	Negative	1	1.32	1.32
	Positive	2	1.54	2.18
	Neutral	4		
VRLTR-67	Negative	2	2.37	2.94
	Positive	2	3.68	4.01
	Neutral	3		
VRLTR-68	Negative	4	4.25*	17.48*
	Positive	2	2.16*	4.34*
	Neutral	1		
VRLTR-69	Negative	1	1.15	1.15
	Positive	2	1.34	1.68

	Neutral	3		
VRLTR-70	Negative	4	6.12*	25.56*
	Positive	2	2.11*	4.26*
	Neutral	2		
VRLTR-71	Negative	4	6.18*	26.83*
	Positive	2	2.01*	4.04*
	Neutral	1		
VRLTR-72	Negative	3	3.06	4.10
	Positive	2	2.34	3.72
	Neutral	2		
VRLTR-73	Negative	4	4.17*	16.71*
	Positive	2	2.08*	4.18*
	Neutral	1		
VRLTR-74	Negative	1	1.16	1.16
	Positive	2	1.19	1.82
	Neutral	3		
VRLTR-75	Negative	1	2.96	2.96
	Positive	1	3.76	3.76
	Neutral	3		
VRLTR-76	Negative	4	2.38	9.56*
	Positive	2	2.04	4.71*
	Neutral	1		
VRLTR-77	Negative	2	3.24	4.59
	Positive	1	3.22	3.22
	Neutral	3		
VRLTR-78	Negative	3	5.33	8.35
	Positive	3	5.62	7.68
	Neutral	1		
VRLTR-79	Negative	3	7.23	21.80*
	Positive	1	3.15	3.15*

	Neutral	3		
VRLTR-80	Negative	4	6.18*	8.81
	Positive	2	3.07*	5.94
	Neutral	1		

*Note: * is more than two-fold difference between positive and negative rank value.*

According to the Wilcoxon rank test, 21 variants of the relative length of telomeric repeats were detected to be associated with coronary heart disease with myocardial infarction: VRLTR-40, VRLTR-41, VRLTR-43, VRLTR-44, VRLTR-46, VRLTR-47, VRLTR-49, VRLTR-51, VRLTR-53, VRLTR-56, VRLTR-59, VRLTR-61, VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71, VRLTR-73, VRLTR-76, VRLTR-79 and VRLTR-80.

During a correlation analysis, for 5 of the 21 detected VRLTR variants, highly significant differences were found between samples of patients with CHD with MI and conditionally healthy study participants (Table 3). In particular, an association of coronary heart disease with old myocardial infarction with variants of the relative length of telomeric repeats VRLTR-46, VRLTR-49, VRLTR-51, VRLTR-53 and VRLTR-56 was identified. At the same time, 6 of 21 variants of the relative length of telomeric repeats (VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71 and VRLTR-73) had a protective effect in coronary heart disease with old myocardial infarction.

IV. CONCLUSION

In the present research work, we propose new markers of coronary heart disease with old myocardial infarction: certain variants of relative length of telomeric repeats (VRLTR). These markers in the studied samples were presented as percentages of the calibrator. DNA isolated from HeLa cells was used as a calibrator.

By measuring variants of the relative length of telomeric repeats in the studied samples, an association of coronary heart disease with myocardial infarction with VRLTR-46, VRLTR-49, VRLTR-51, VRLTR-53 and VRLTR-56 was detected. At the same time, 6 of 21 variants of the relative length of telomeric repeats (VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71 and VRLTR-73) had a protective effect in coronary heart disease with myocardial infarction.

Table 3: Correlation of Variants of the Relative Length of Telomeric Repeats with Coronary Heart Disease with Old Myocardial Infarction

Number	Variants of the relative length of telomeric repeats	Correlation coefficient	Asymptomatic significance (two-sided)
1	VRLTR-40	0.211	0.101*
2	VRLTR-41	0.302	0.064*
3	VRLTR-43	0.287	0.071*
4	VRLTR-44	0.218	0.096*
5	VRLTR-46	0.609	0.001**
6	VRLTR-47	0.305	0.068*
7	VRLTR-49	0.591	0.002**
8	VRLTR-51	0.610	0.001**
9	VRLTR-53	0.554	0.003**
10	VRLTR-56	0.621	0.001**
11	VRLTR-59	-0.312	0.056*
12	VRLTR-61	-0.306	0.068*
13	VRLTR-63	-0.608	0.001**
14	VRLTR-65	-0.615	0.001**
15	VRLTR-68	-0.425	0.043**
16	VRLTR-70	-0.554	0.036**
17	VRLTR-71	-0.482	0.031**
18	VRLTR-73	-0.542	0.042**
19	VRLTR-76	-0.244	0.076*
20	VRLTR-79	-0.267	0.071*
21	VRLTR-80	-0.326	0.054*

*Note: * is highly significant correlation of mutations with CHD with MI (p≤0.05);*
*** is correlation of mutations with coronary heart disease with myocardial infarction at the level of significance p≤0.1.*

Author Contributions

Conceptualization, M.A.S.; methodology, M.A.S.; validation, A.I.R. and M.D.S.; formal analysis, M.A.S. and M.D.S.; investigation, M.A.S., N.A.D., M.D.S. and A.I.R.; resources, A.Yu.P., T.I.K., I.A.S., D.F.B. and A.V.Ch.; data curation, M.A.S, N.A.D. and M.D.S.; Writing – Original Draft Preparation, M.A.S., M.D.S., N.A.D., A.I.R., P.P. and D.M.; Writing – Review & Editing, V.P.K., M.A.P. and A.Yu.P.; Project Administration, A.N.O. and V.N.S; Funding Acquisition, A.N.O.

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Institutional Review Board Statement

The study was performed in accordance with the principles outlined in the Declaration of Helsinki of 1975 and its revised version of 2013. The study protocol was approved by the Institute for Atherosclerosis Research Committee on Human Research, Moscow, Russia, protocol No. 078-15 of September, 08, 2015.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability statements

The datasets presented in this article are not readily available because the data are part of an ongoing study of patients with cardiovascular diseases from Russia.

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Conflict of interests

The authors declare no conflict of interests. The material for the investigation has never been published before.

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Portrait of Female Mortality at Fertile Age between 2018 and 2022 in a City in Southern Brazil: A Comparative Study

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ABSTRACT

In Brazil, women represent 51.5% of the population and play multiple roles, including family care and household chores, which directly impacts their health. IBGE data indicates that women are the main users of health services, accounting for 78% of users. Corroborating their role in modern society, there have been changes in the mortality profile of women, which is the focus of this study. The aim of the study was to analyze the main causes of mortality among women of childbearing age in a municipality in the interior of the state of Rio Grande do Sul, making a comparison with a previous study carried out by the authors. The data shows that 197 deaths were recorded, with a higher prevalence in the 40-49 age group. The main causes of death were neoplasms, circulatory diseases, infectious diseases and external causes. This suggests the need for health promotion, early diagnosis and appropriate treatment of diseases to prevent early mortality, highlighting the importance of public health policies.

Keywords: mortality; woman; women's health; neoplasm.

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In Brazil, women represent 51.5% of the population and play multiple roles, including family care and household chores, which directly impacts their health. IBGE data indicates that women are the main users of health services, accounting for 78% of users. Corroborating their role in modern society, there have been changes in the mortality profile of women, which is the focus of this study. The aim of the study was to analyze the main causes of mortality among women of childbearing age in a municipality in the interior of the state of Rio Grande do Sul, making a comparison with a previous study carried out by the authors. The data shows that 197 deaths were recorded, with a higher prevalence in the 40-49 age group. The main causes of death were neoplasms, circulatory diseases, infectious diseases and external causes. This suggests the need for health promotion, early diagnosis and appropriate treatment of diseases to prevent early mortality, highlighting the importance of public health policies.

RESUMO

No Brasil, as mulheres representam 51,5% da população e desempenham múltiplos papéis, incluindo cuidados familiares e tarefas domésticas, o que impacta diretamente sua saúde. Dados do IBGE indicam que as mulheres são as principais usuárias dos serviços de saúde, sendo 78% dos usuários. Corroborando com seu papel na sociedade moderna, observa-se mudanças no perfil de mortalidade das mulheres, sendo esse o foco do presente estudo. O objetivo da pesquisa foi analisar as principais causas de mortalidade das mulheres em idade fértil em um município do interior do estado do Rio Grande do Sul, realizando um comparativo com uma pesquisa prévia realizada pelas autoras. Os dados apontam que foram registrados 197 óbitos, com maior prevalência na faixa etária de 40 a 49 anos. As principais causas de morte foram neoplasias, doenças circulatórias, doenças infecciosas e causas externas. Desse modo, sugere-se a necessidade de promoção da saúde, diagnóstico precoce e tratamento adequado de doenças para prevenir a mortalidade precoce, destacando a importância de políticas públicas de saúde.

Keywords: mortality; woman; women's health; neoplasm.

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I. INTRODUCTION

The trajectory of women in the history of the modern world is marked by struggles in search of greater space and autonomy in society, especially since the 20th century with the advance of the feminist movement. In this way, women have achieved more and more civil, political, social, economic and cultural rights, including becoming the majority of the Brazilian population[1] [2] [3]. According to the latest census by the Brazilian Institute of Geography and Statistics (IBGE, 2023), women make up 51.5% of the country's population. In this scenario, it can be seen that women play a variety of roles, as well as being involved in family care and household chores. The

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accumulation of functions, changes in behavior patterns and women's new lifestyle habits over the years have had a direct impact on their health, contributing to increased exposure to risk situations[1] [2] [3]. It is worth noting that this population group is the one that uses health services the most, both public and private, accounting for 78% of total users [3].

Against this backdrop, it can be seen that the pattern of female mortality has changed, especially from the industrialization process to the present day. Currently, women are more exposed to stress and risk factors for chronic diseases, such as a sedentary lifestyle, obesity, smoking and increased alcohol use [1] [3]. These factors, together with increased exposure to external risks such as homicides and traffic accidents, have contributed to female mortality. Studies carried out in different global locations highlight a worrying scenario: inequalities based on gender issues, linked to factors such as lower income, lower educational levels and reduced access to employment. These factors limit women's ability to take proper care of their own health [3].

In this context, outlining the profile of risk factors for female mortality broadens and promotes more effective discussions about women's health. The study of mortality in this specific group is a crucial health indicator, making it possible to analyze the various contexts of the health/disease process. This can support the planning, management and evaluation of public policies, providing a solid basis for more precise and effective interventions[1] [3]. In addition, authors point out that mortality is a vital indicator for formulating public health policies, providing a comprehensive view of the specific needs of this population. Thus, analyzing female mortality is a means of better understanding the health conditions and disparities that affect women[4].

For this analysis, it is important to consider that exposure to sexual and reproductive risks in the country occurs in the 10-49 age group, with women within this range defined as being of childbearing age. This definition differs slightly from the reproductive period considered by the World Health Organization (WHO), which covers the 15-44 age group. Paying attention to the causes of female mortality during reproductive age makes it possible to identify the greatest risks to which women are exposed during this period of their lives, making it possible to plan health promotion actions, early diagnosis and appropriate treatment of diseases, with the aim of avoiding early mortality. In this sense, when we look at sexually transmitted infections and cancer, in Brazil there are still late diagnoses in various regions, highlighting a weakness in the health system that directly affects women [1] [3].

Taking this as a basis, this article aims to compare the causes of mortality of women of childbearing age (WCA) with a previous study carried out by the authors in 2019, which considered the analysis of WCA deaths from 2013 to 2017. The current proposal was based on an analysis of the same five-year period, considering the years 2018 to 2022, in the same location. The aim was to analyze and discuss the issue based on current theoretical references, in order to promote health promotion measures, disease prevention and early mortality.

The following pages will therefore set out and work on the results, dividing the writing into the following sections: Method, Results, Discussion and Conclusion.

II. METHODS

To carry out this research, the method chosen was a demographic time-series epidemiological study with an exploratory descriptive approach. This aims to identify the causes of diseases and their risk factors by investigating and distributing the causes of mortality in a specific population, in this case, the FIM. Within a given time frame and location, the observed data is described and it is thus possible to contextualize and identify the main causes of mortality with the aim of fostering strategies for health promotion and prevention of early mortality in the group in question.

The data was collected from the DATASUS TABNET Information System for the period May 2024. This Ministry of Health system provides, among other things, epidemiological data on morbidity and mortality, important health

indicators that serve to support analysis and decision-making in collective health actions. The data was selected by defining the period - from 2018 to 2022 -, the age - from 10 to 49 years -, the female sex and the chapters of the ICD 10 - International Classification of Diseases. Since the focus of the study was to follow up the subsequent years of the previous research with the aim of analyzing whether there was a change in the mortality pattern of FIM in the same municipality, in the interior of Rio Grande do Sul, and to bring new discussion on the subject together with current references from other authors.

The quantitative data was then organized into spreadsheets, in which the relative and absolute frequencies were calculated in order to organize the data to support the analysis and subsequent discussion. Next, the information generated was discussed and problematized based on theoretical references, then compared with the study carried out by the authors in 2019. Based on the four most frequent underlying causes of death, which will be explained in the results.

It should be noted that in the previous study, the data was collected from the Mortality Information System (SIM) of the municipality in question. At the time of the previous production, it was possible to have contact with the death certificates entered in this system, making it possible to obtain more detailed data, such as the neighborhood of residence and work activity of the group surveyed.

III. RESULTS

From the data collection and analysis, it was observed that in the years 2018 to 2022, 5,812 total deaths were registered in the municipality of Santa Cruz do Sul, of which 2,830 (48.7%) were female deaths. Within this group, 197 (6.9%) were women of childbearing age. Deaths occurred most frequently in the 40 to 49 age group (54.3%), followed by the 30 to 39 age group (28.4%) and less frequently in the 20 to 29 age group (12.7%) and the 10 to 19 age group (4.6%). The average recorded was 39.4 FIM deaths per year, with an overall FIM mortality rate for the five-year period of 1.47 deaths per 1000 FIM.

Regarding race/color, there was a higher prevalence among white women (80.2%), followed by black women (11.2%), brown women (8.2%) and yellow women (0.5%). No deaths were recorded among indigenous people. In terms of schooling, the majority had between 8 and 11 years of study (54.8%), followed by 12 years or more (17.8%) and 4 to 7 years (15.7%). There were also 6.6% of FIM deaths with no schooling. It should be noted that there was no record of schooling in 5% of the deaths that occurred in the period, which implies an unreliable analysis of the indicator in the years covered by this study. With regard to underlying causes of death, there were four main causes: neoplasms (28%), followed by diseases of the circulatory system (18%), some infectious and parasitic diseases (16.7%) and external causes (13%). It should be noted that in the period analyzed, although not very prevalent, but as an important indicator of maternal health, FIM deaths were recorded due to causes related to pregnancy, childbirth and the puerperium, equivalent to 2% of total deaths. Other varied causes of mortality were also recorded to a lesser extent.

The main neoplasms found were those of the female genital organs (32.7%), which include the uterus, various genital organs, cervix, vulva, vagina and fallopian tubes, followed by breast cancer (23.6%). Together, these typically female neoplasms accounted for more than half of all FIM cancer deaths recorded in the period (56.3%). It's worth noting that other neoplasms, not typically female, were also recorded, but at a lower prevalence. As for diseases of the circulatory system, cerebrovascular diseases (44.4%) and ischemic heart diseases (38.8%) stood out. With regard to the causes of infectious and parasitic diseases, the finding was "other viral diseases not classified elsewhere" (60.6%), followed by HIV (27.7%). With regard to external causes, the highlight in the period surveyed was traffic accidents (69%).

IV. DISCUSSION

The municipality surveyed is located in the interior of the state of Rio Grande do Sul, 155 kilometers from the capital Porto Alegre and is in the region called Vale do Rio Pardo, in the central region of the state. According to the IBGE census (2020), the city has 131,365 inhabitants and is a global hub for the tobacco industry, with tobacco as its main source of income; in addition to industries in the food, metallurgical and pharmaceutical sectors. The municipality currently ranks 5th in the state in terms of Gross Domestic Product (GDP).[5]

It should be noted that the four main causes of mortality identified in the group studied have been observed over the years in studies carried out to date. For example, in 1986, the first study on FIM mortality was carried out in the city of São Paulo and the causes found were circulatory system diseases, neoplasms, external causes, infectious and parasitic diseases and maternal causes, in descending order [2]. It is estimated that over the decades there will be a growing increase in deaths from neoplasms, overtaking cardiovascular causes. According to the WHO, this scenario is becoming increasingly frequent on a global level, highlighting cancer as a major health problem [1].

In this sense, the mortality coefficients are higher in the 40-49 age group, followed by the 30-39 age group. This data is no different from previous research, as well as being a finding in all the studies analyzed in this discussion[1 2 3 6]. It should be emphasized that even though there is a gradual increase in the number of deaths in the older age groups, we are still talking about a relatively young female population, thus configuring an important indicator of something that is a public health problem [3].

With regard to race, it is important to consider the colonization process of each region. In this study, mortality was more frequent among whites, but it is clear that the municipality in question is Germanic. This data may differ from the race profile of FIM found in other studies carried out in different Brazilian states and cities, where the highest frequency of morality appears among black and brown people[1 7].

This data is similar to a study carried out in the state of Sergipe[6], where the highest mortality coefficient was also found among white women, as well as those with more years of schooling, the same finding as in this study. This information suggests that not only women with less schooling are affected by the causes of early mortality, since populations with less schooling can point to poor social conditions and less access to health information[8], contributing to the progression of comorbidities and consequently death. However, even women with greater access to education have been affected by these problems.

Focusing on the causes of mortality, neoplasms continue to be the main cause, especially in the 30-49 age group. This has appeared in both developed and developing regions. It should be emphasized that this comorbidity requires early diagnosis and intervention for proper treatment in order to achieve a better prognosis, with a greater chance of cure [3 1]. And although there are significant differences in the pattern of cancer mortality in different regions of Brazil [1], typically female neoplasms stand out when the focus is on analyzing women's health. Although breast cancer stands out as the main neoplasm of mortality in the country, the advance of cervical cancer has worried health authorities. For example, since 2016, the state of São Paulo has seen a trend reversal in cervical cancer mortality [8].

Os fatores que têm modificado o quadro epidemiológico dessa doença no Brasil precisam ser analisados e estudados, mas algumas hipóteses podem explicar esse fato. Há uma maior incidência de câncer do colo do útero nas regiões menos desenvolvidas, mas esse padrão está mudando e um aumento da prevalência também tem sido observado nos países desenvolvidos, embora as causas dessa mudança ainda estejam sendo estudadas[8]. The National Cancer Institute (INCA) highlights the magnitude of this disease, revealing that new cases reach 530,000 per year worldwide[9]. The increase in cervical cancer, especially in young women, can be explained by the change in sexual behavior, which is justified

by the increased freedom exercised by women, coupled with low adherence to the use of methods of protection against sexually transmitted infections. Within this context, the main cause of this neoplasm is infection by the human papillomavirus (HPV)[8].

HPV infection is the most common sexually transmitted infection in the world. Women over the age of 30 who are sexually active end up being the group most exposed to the virus. Subtypes 16 and 18 are responsible for 60% and 15% of cervical cancer cases, respectively, with an increasing trend in mortality rates[10]. It is therefore possible to address the need for primary prevention, which takes place through health education, emphasizing the importance of using condoms during sexual relations and encouraging vaccination. These two simple measures help to reduce the spread of virus[10].

It is important to emphasize that it is necessary to invest efforts in public health policies to control the disease; in this context, the importance of a strengthened and active primary health network in communities is highlighted. In Brazil, the Unified Health System (SUS) is guided by the principles of universality, integrality and equity and is organized on a territorial basis, taking into account the regionalization and decentralization of the places where it is inserted, since each territory has its own specificities. This gives rise to the health system's levels of care, which are defined as primary (basic), secondary (specialized) and tertiary (highly complex). These categories follow an ascending order to ensure that each individual is cared for at the level they need at the time[11].

On the other hand, mortality from cervical cancer is considered avoidable since this neoplasm has great potential for cure. Therefore, if it is diagnosed at an early stage[1], through screening tests, it is possible to change the context of mortality, since the scenario may point to a failure in screening practices and early diagnosis[8].

It's worth noting that the time between infection and the development of cancer is long, and is more aggressive in young women[10]. This population is made up of economically active women, who work and take on various responsibilities in the modern world. Consequently, this group has less free time to carry out adequate screening[8] , pointing to a longer time between screenings[10]. This may justify the discovery of the disease at an advanced stage and consequently reduce the chances of cure and increase the chances of mortality. Like cervical cancer, breast cancer is also a neoplasm that has a good potential for cure when diagnosed in good time. There is still a notable increase in the rates of this disease in various regions around the world, making it a public health problem that is not exclusively Brazilian. It is therefore clear that there is a need to expand the coverage of screening and early detection in the health system. [1]

It's worth broadening the discussion beyond typically female neoplasms and turning our attention to cardiovascular diseases. Since diseases in this group are increasingly affecting the female population of reproductive age all over the world, this has been observed in all the sources consulted. When compared to men, the mortality rate ends up being higher, since women have symptoms that are different from the classic symptoms, for example in coronary syndromes, because the physiology of the disease is different, causing inflammatory changes in the coronary endothelium in women, unlike the male population, which has obstructive lesions [1].

Regarding the third and fourth causes identified respectively, infectious and parasitic diseases, with emphasis on "other virus diseases not elsewhere classified", the complexity of the debate involving this topic can be seen. Given that this classification simultaneously covers a variety of viruses, it is not clear which ones these are, raising doubts as to whether the covid-19 virus would be included in this unspecified group, given that the period analyzed saw a global pandemic causing thousands of deaths, also affecting FIM. Finally, among the external causes of mortality, traffic accidents stand out. In Brazil there has been an increase in mortality due to this factor, with a significant increase in the last decade, placing the country in third place in the ranking of

traffic deaths. Considering the panorama of modern women, this cause is increasingly affecting the female mortality profile[12 13].

V. CONCLUSION

Considering the aim of the study was to carry out a comparative analysis with the first study carried out by the authors, the new study shows a change in the mortality pattern of FIM. It is worth noting that the main causes found are not restricted to the municipality in question, since these data corroborate the global research scenario on the subject.

Although the distribution of causes of mortality has changed, both in the previous study and in the others analyzed - cited in the references - with regard to women's health, there is a clear need for health promotion, as well as prevention and early detection of neoplasms, especially those that are typically female. This group of diseases is the most prominent in the epidemiological data available on the subject globally.

Based on the results and discussion, we encourage further studies in the area so that we can better understand the issues surrounding women's health and thus broaden the way in which care for modern women of reproductive age is thought of.

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Treatment of Recurrent Basilar Artery Aneurysms at Fenestration after Coils using Flow Diverter Combined with Coils: Case Report

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SUMMARY

An aneurysm at the fenestration position of the basilar artery is an extremely rare condition that presents challenges in treatment. Aneurysm recurrence is a complication that can occur after interventions for aneurysms in this location. We report the case of a 43-year-old male patient with a ruptured basilar artery aneurysm treated with coils. After 30 months of follow-up, the aneurysm recurred and was treated with a flow diverter stent combined with coils.

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An aneurysm at the fenestration position of the basilar artery is an extremely rare condition that presents challenges in treatment. Aneurysm recurrence is a complication that can occur after interventions for aneurysms in this location. We report the case of a 43-year-old male patient with a ruptured basilar artery aneurysm treated with coils. After 30 months of follow-up, the aneurysm recurred and was treated with a flow diverter stent combined with coils.

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I. INTRODUCTION

Basilar artery fenestration has a reported incidence ranging from 0.6% to 2.33%, depending on the modality used to study this variant. When basilar artery fenestration is present, associated aneurysms are rare, with a reported incidence of 0.33% of all intracranial aneurysms[1]. Currently, using coils to treat ruptured brain aneurysms has been proven to be a safe and effective treatment method. The main problem with this treatment method is the significant rate of incomplete occlusion of the aneurysm or the possibility of the aneurysm recurring after intervention over time, with the risk of aneurysm rupture causing recurrent bleeding[2]. According to the literature, aneurysm recurrence or aneurysm neck reopening occurs in approximately 20% of patients, requiring retreatment in approximately half of them[3]. However, there is no consensus or specific recommendation regarding retreatment after aneurysm coiling treatment. The use of flow-diverting stents in the treatment of posterior circulation aneurysms in general, and in the treatment of recurrent posterior circulation aneurysms after coils, is still controversial.

We discuss the case of a 43-year-old male patient who underwent coil intervention for a ruptured basilar artery aneurysm in August 2021. Thirty months after the initial treatment, an MRI scan showed aneurysm recurrence (approximately 7 mm in size), confirmed by DSA. The patient was then successfully treated with flow-diverting stents combined with coils.

II. CASE REPORT

A 43-year-old male patient was admitted to the hospital in August 2021 because of a subarachnoid hemorrhage around the brainstem and in the fourth ventricle (Fisher grade 3) due to a ruptured aneurysm at the basilar artery fenestration site (Figure 1).

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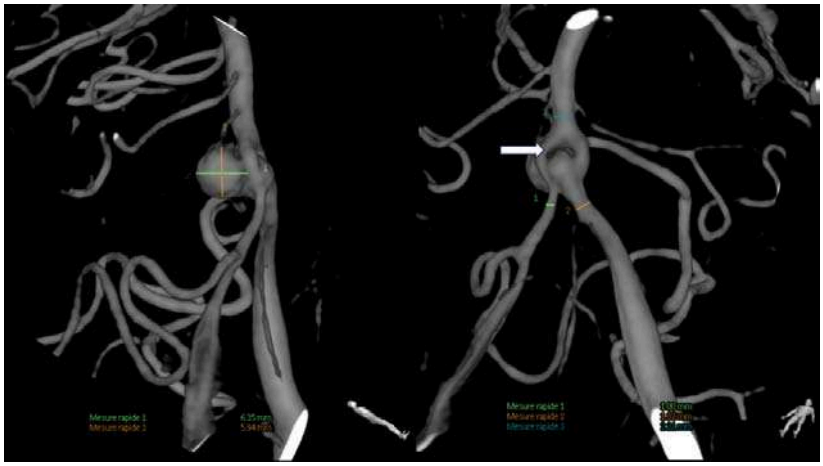

Figure 1: Aneurysm at the Basilar Artery Fenestration Site (arrow)

The patient was subsequently treated with coils under digital subtraction angiography (DSA). The procedure immediately showed complete occlusion of the aneurysm (Figure 2).

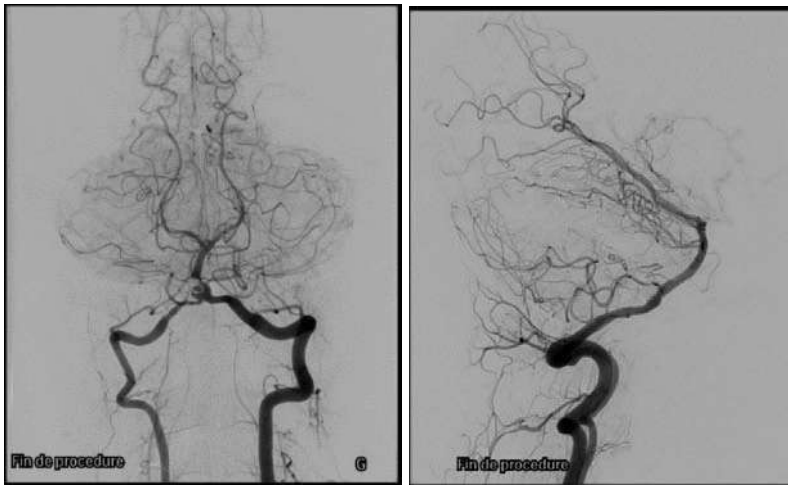

Figure 2: Dsa Scan Checked after the First Coil Button in August 2021, No Residual Bulge was Seen

Thirty months after initial treatment, MRI revealed a recurrence of the aneurysm (approximately 7 mm in size) confirmed by DSA (Figure 3).

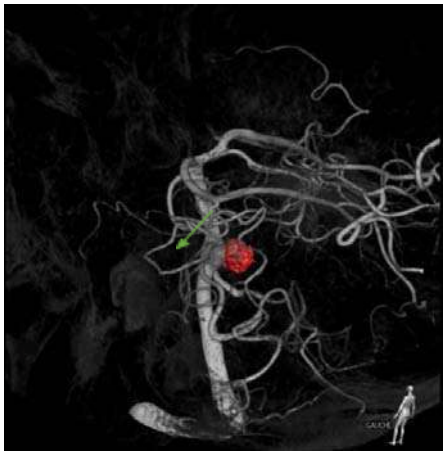

Figure 3: Dsa Scan Shows A Recurrence of the Aneurysm at the Neck of the Old Aneurysm (Blue Arrow) and the Old Aneurysm has Been Occluded with Coils (Highlighted In Red)

The patient was then successfully treated with a flow-reversing stent combined with coils. Endovascular intervention with access through the bilateral femoral artery, placing 01 8F sheath in the right femoral artery and 01 6F sheath in the left femoral artery. Place Phenom 21 into the basilar artery and Echelon 14 into the aneurysm. We chose the p64-MW 3.5 x 15 mm flow diverter following simulations with Sim and Cure. This is placed at the lower end of the basilar artery up to the left V4 segment to cover the aneurysm neck. Place 2 Optima coils into the aneurysm. DSA check immediately after intervention and cranial MRI 3 months after intervention showed complete occlusion of the lesion (Figure 4).

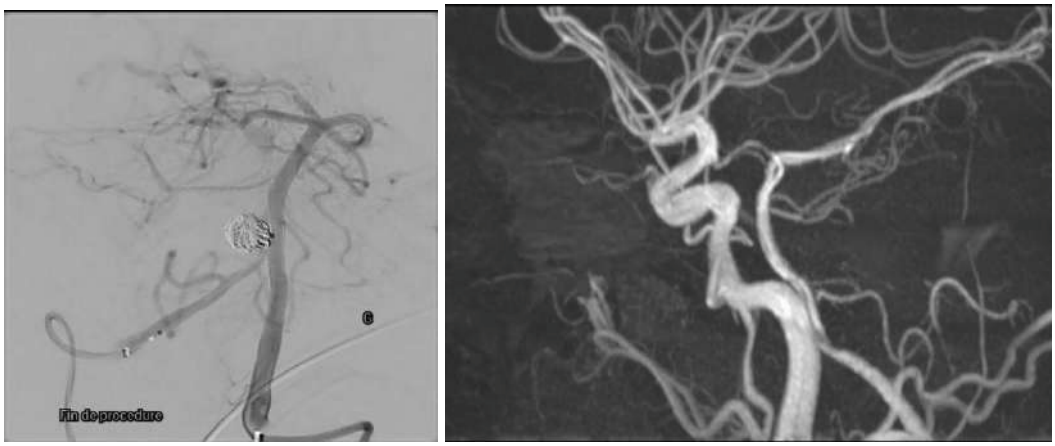

Figure 4: Dsa Scan after Stent and Coil Placement Shows No Residual Bulge (A). Magnetic Resonance Image After 3 Months on Tof 3d Pulse Sequence Shows No Residual Bulge (B)

III. DISCUSSION

After the anterior communicating artery, the basilar artery is the second most common site of fenestration, with the rate of basilar artery fenestration ranging from 1% to 2.07% on magnetic resonance imaging, 0.28% to 6% at autopsy, and 0.02% to 0.6% on digital subtraction angiography[4,5,6,7]. When basilar artery fenestration is present, associated aneurysms are rare, with a reported incidence of 0.33% of all intracranial aneurysms[1]. Posterior circulation aneurysms in general, and basilar artery aneurysms in particular, pose significant challenges for interventionalists and neurosurgeons due to the complexity and special anatomical location of these lesions.

In recent years, endovascular treatment has been considered the "gold standard" for intracranial posterior circulation aneurysms due to its lower procedural complication rate compared with surgery[8]. However, long-term post-intervention follow-up studies of posterior circulation aneurysms embolized with coils show a high rate of aneurysm recurrence or aneurysm neck reopening, estimated at about 20% of patients, with retreatment required in about half of them[3].

In our case, the patient initially had a ruptured aneurysm at the proximal end of the basilar artery, right at the proximal fenestration site of the basilar artery. The patient was then successfully treated with coils, and it seemed that the aneurysm was completely occluded. No residual aneurysm was seen on the DSA scan after the first intervention. However, 30 months later, there was a recurrence of the aneurysm at the neck of the old aneurysm. Choosing a treatment plan in this case was very difficult. In the literature, there is no consensus or specific recommendation regarding the retreatment of recurrent aneurysms after aneurysm coil treatment.

Endovascular treatment seems to be a more optimal option than surgery in this case. The use of flow-diverting stents in the treatment of recurrent posterior circulation aneurysms after coils is controversial. Using stents alone or combining stents and coils helps increase treatment effectiveness and reduce the risk of

recurrence, but the risk of stent occlusion and early bleeding after intervention increases in these patients[9].

In our case, the patient was successfully treated with endovascular intervention, combining coils and flow-diverting stents, with no complications of embolism or early aneurysm rupture after intervention. Post-intervention check-up and follow-up after 3 months showed that the recurrent aneurysm had been completely occluded.

The progression of a brain aneurysm after intervention is unpredictable, making post-treatment follow-up crucial yet challenging. There is ongoing debate about whether long-term follow-up imaging should be performed after intervention and which imaging modality should be used. Digital subtraction angiography (DSA) is considered the gold standard for monitoring, but it has several disadvantages, including the risk of complications during the procedure due to its invasive nature and the risk of radiation exposure to the patient.

Magnetic resonance imaging (TOF 3D) is a suitable technique for monitoring post-intervention cerebral aneurysms. The Clinical Practice Guideline Committee of the KoNES (2024) recommends that CE-MRI or TOF MRA imaging be used to monitor patients 3-6 months after intervention, then at 1, 2, 4, and 6 years after treatment. Computed tomography angiography (CTA) is commonly used to evaluate intracranial arteries due to its lower cost and shorter scanning time compared to MRA. However, CTA involves the use of a contrast agent and radiation exposure, and post-intervention materials such as coils and stents can interfere with imaging[0].

Regardless of the technique, it is important to provide morphological information, including whether the aneurysm is completely occluded and whether there is any remaining neck or part of the aneurysm. There is no optimal imaging tool to evaluate residual or recurrent aneurysms fully. Regarding timing, follow-up imaging should be performed 3–6 months after treatment, and then over a range of 12 to 18 months. Subsequent follow-ups vary from center to center and must be tailored to the condition of the lesion after intervention.

IV. CONCLUSION

In summary, recurrence after treatment of brain aneurysms, particularly in the posterior cerebral artery system, is a risk that requires long-term monitoring. Treating recurrent aneurysms with flow-diverting stents combined with coils is a feasible, safe, and effective method, although it carries certain risks, such as premature aneurysm rupture or stent blockage after intervention.

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Impact of the Ebola Virus Outbreak on Tuberculosis Treatment Adherence and Outcomes in a Military Hospital in Freetown, Sierra Leone

Kathryn M. Hogan, Henry Saidu Bangura, Jing Li, Mohamed Akmed Salim Kamara, Jiafu Jiang & Michael E. von Fricken

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ABSTRACT

Introduction: The impact and disruption of infectious disease outbreaks stretch far beyond their direct death toll, as they often overburden health systems, reduce treatment seeking behaviors, and interrupt treatment regimens. This study examines the impact of the 2014–2016 Ebola virus outbreak on tuberculosis (TB) treatment outcomes at the 34 Military Hospital in Freetown, Sierra Leone.

Methods: We used retrospective data from 1,085 TB patient outcome data registers to build a multinomial logistic regression model to evaluate the change in TB treatment outcomes before and after the Public Health Emergency of International Concern (PHEIC) declaration in August 2014.

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Methods: We used retrospective data from 1,085 TB patient outcome data registers to build a multinomial logistic regression model to evaluate the change in TB treatment outcomes before and after the Public Health Emergency of International Concern (PHEIC) declaration in August 2014.

Results: These results showed that HIV status, patient age, whether patients had active versus latent TB, and the time since the start of the outbreak were significantly associated with TB treatment outcomes.

Discussion: The model showed an increase in probability of unknown and unsuccessful (died or treatment failed) treatment outcomes with each month after the PHEIC declaration, across age groups, TB status, and HIV status.

I. INTRODUCTION

The 2014–2016 Ebola virus (EVD) outbreak was devastating to West Africa, causing an estimated 28,616 cases and 11,310 deaths as of June 2016, as well as a number of indirect health consequences.[1] The outbreak originated in Guinea, where the first recorded case was reported in December 2013.[2] Cases continued to spread along the country borders and into Liberia and Sierra Leone, increasing rapidly by May 2014.[2] Ebola virus swept through Sierra Leone communities, leading to an estimated 14,124 cases and 3,956 deaths, representing nearly half of all cases in West Africa.[1] Although these high case numbers and death rates emphasize the severity of the outbreak, they do not capture the extent of indirect deaths that may have occurred as a result of disrupted health systems for other diseases such as tuberculosis (TB) and HIV.[3,4]

During the EVD outbreak, Sierra Leone's health care services were overburdened and understaffed.[5] People were reluctant to seek treatment at health centers due to widespread fear of infection and discrimination, closures of health facilities, and the implementation of new curfews, laws, and border closures.[4,6] Healthcare workers (HCWs) in Sierra Leone also experienced a disproportionate burden of EVD infections, with 28% of 1,100 total HCWs infected, 72% of whom died.[7] Cases among HCWs peaked 3 to 4 weeks before the overall peak of the EVD outbreak, reducing the number of available medical personnel to provide care, and posing an additional challenge to containing the outbreak.[7,8] The frequency of nosocomial infections also created fear and public distrust surrounding healthcare facilities.[9]

The EVD outbreak also impacted treatment-seeking behaviors for other prevalent diseases

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that require continuous care, such as TB and HIV. Before the EVD outbreak, Sierra Leone experienced the third highest TB incidence in the world, as well as an HIV prevalence of 54,708, which increases the likelihood of latent TB infection (LTBI) reactivation.[10–12] In 2012, there was a reported incidence of 674 TB cases per 100,000 people and prevalence of 1,300 TB cases per 100,000 people. [13] In 2013 and 2014, Sierra Leone registered an average of 12,000 to 13,000 cases of TB each year, with treatment completion rates estimated at 85% to 87%.[13,14]

During the EVD outbreak, directly observed therapy short course (DOTS) programs for TB were interrupted, shortages in HIV drugs occurred, and patients undergoing TB and/or HIV treatment were disengaged.[7] After the height of the outbreak, issues related to the repurposing of clinical teams and facilities to respond to the outbreak, along with a "no touch" policy, decreased accessibility to DOTS for TB.[8] Given the possibility of an estimated reduction in treatment accessibility of 50% due to the EVD outbreak, it is predicted that the deaths attributed to HIV and TB would increase by 9% and 61%, respectively, in Sierra Leone.[4] Considering each of these integrated factors impacting TB treatment access during the EVD outbreak, the potential for increases in deaths is substantial.

These numbers become increasingly important in understanding the broader implications of epidemics given the ongoing COVID-19 pandemic, which will likely cause similar diagnostic and treatment interruptions worldwide.[15] To better understand the potential impacts that treatment interruptions may have on diseases such as TB, it is vital to use existing information from previous outbreaks. This study uses retrospective TB patient outcome data, paired with HIV status, from a military hospital in Freetown, Sierra Leone, to quantify the impact of the 2014 EVD outbreak on TB treatment outcomes. The study applies a robust modeling framework to understand which patient characteristics influenced TB treatment outcomes during the Ebola epidemic and to determine how the influence of those factors on predicted treatment outcomes changed through time.

II. METHODS

a) Study Design and Setting

This retrospective study reviewed TB patient outcome data from the 34 Military Hospital in Freetown, the capital of Sierra Leone. The two-tier health care system in Sierra Leone is composed of Peripheral Healthcare.

Units and secondary care consisting of three referral hospitals, 21 district hospitals, 27 private hospitals, and 45 private clinics, most of which are located in Freetown.[16] The 34 Military Hospital is one of three referral hospitals in Freetown, providing service to 200 to 250 patients per day.[17] The hospital is located at Wilberforce Barracks and serves 25% of the western section of Freetown, including soldiers, their families, and the general population. It is a teaching and general hospital, with 369 personnel. A study from 2011 to 2014 indicates that the 34 Military Hospital consisted of four departments, a laboratory facility, and staffed 17 permanent military Medical Officers, three specialists, and five consultants at the time of this study.[17] As part of a Frontline Field Placement Surveillance Report, data were extracted from Patient Hospital Register TB Records between January 3, 2012, to December 22, 2016, and included in this analysis. Coinfection with HIV was also examined as a variable of interest related to patient outcomes. The declaration of a Public Health Emergency of International Concern (PHEIC) on August 8, 2014, was used as the distinguishing start date of the EVD outbreak throughout the following analyses.[16]

b) Pearson's Chi-Square Tests

Patient data was grouped into two categories based on the individual's enrollment date: pre- and post-PHEIC.[18] Frequency tables were calculated containing treatment outcomes based on pre- or post-PHEIC status. which were then used to calculate a Pearson's χ^2 test probability of treatment outcomes based on a patient's pre- or post-PHEIC enrollment status. Separate Pearson's χ^2 tests were run for both active and latent tuberculosis patients. The null hypothesis was no association between pre- or post-PHEIC enrollment status and treatment outcome.

c) Regression Analysis

To further quantify the impact the EVD outbreak may have had on TB treatment outcomes at 34 Military Hospital, this study used a multinomial logistic regression model (see Supplemental Information).[19] For each patient record, we quantified the number of months since the PHEIC declaration on August 8, 2014, at which point 717 cases were confirmed in Sierra Leone.[1,18] The variable "months after outbreak" for all patient records with entry dates between January 3, 2012 and August 8, 2014, were set to the value of zero. Treatment outcomes were included in hospital records in the following categories: cured, completed, defaulted, died, failed, lost to follow-up, transferred, and unknown. Because of the limited clarity related to the definitions of the outcome data reported, outcomes were reclassified based on the objectives of this paper and merged into the following groups: "successful" (completed or cured), "unsuccessful" (died or failed), "lost to follow-up" (lost to follow-up, abscond, or default), and "unknown" (unknown or transferred).[20]

A series of multinomial logistic regressions were performed to evaluate the change in treatment outcomes following the PHEIC declaration. The full model included the following variables: HIV status, sex, age, TB type (active or latent), and the number of months after the outbreak. An interaction term between age and HIV status was also tested under the hypothesis that the effect of HIV status on treatment outcome could vary depending on the patient's age. All explanatory variables were examined for collinearity before inclusion in the model, using a cutoff correlation of 0.60 to be included. After constructing the full model, the model was tested for any violations of the independence irrelevant alternatives (IIA) assumption of multinomial logistic regression models by conducting a Hausman diagnostic test, following the procedure outlined by Kwak and Clayton-Matthews (2002).[19] Under the Hausman diagnostic test, the treatment outcomes were dropped one at a time from the data set, and coefficients were recalculated using the constrained model, with the full set of covariates.[19] Because the coefficients of each of the constrained models were statistically identical to the relevant coefficients of the full model, the IIA assumption was satisfied.

The model selection process was conducted using an information theoretic approach.[21] A backward-stepwise process was used, dropping one covariate at a time to determine which model resulted in the lowest Akaike information criteria (AIC) value.[21] Covariates were dropped until eliminating any other covariate from the model would result in a higher AIC value, and the resulting model was chosen as our optimal model. Multinomial logistic regressions were calculated using the *multinom* function in the *nnet* package in R, version 3.6.1.[22,23]

III. FINDINGS

a) Study Group Demographics and Descriptive Data

After patients without an enrollment date were removed (N = 1), records from 1,085 patients remained (Table 1) that were used for the regression and χ^2 analyses. The mean patient age was 35.57 years old (SD = 18.61) with a range of 58 days to 98 years old. Regarding HIV status, 679 patients (62.58%) were HIV negative, 290 patients (26.73%) were HIV-positive, and 116 patients (10.69%) were not tested for HIV.

Overall, 377 patients (34.75%) were female, and 708 patients (65.25%) were male. There were 711 patients with successful outcomes, 250 who were lost to follow-up, 89 with unsuccessful outcomes, and 35 with unknown outcomes. Patients were split by TB status, with 553 patients (50.97%) classified as having active TB and 532 patients (49.03%) having latent TB. Of the 553 patients with active TB, 72.33% were successful, 18.44% were lost to follow-up, 6.51% were unsuccessful, 2.71% had unknown outcomes. Of the 532 patients with latent TB, 58.46% of outcomes were successful, 27.82% were lost to follow-up, 3.76% had unknown outcomes, and 9.96% were unsuccessful outcomes.

Table 1: Demographic Information from Patients with Tb (N = 1,085) at 34 Military Hospital in Freetown, Sierra Leone, from 2012 to 2016

Demographics Sex	Pre- PHEIC, *n* (%)	Post- PHEIC, *n* (%)	Total population, N = 1,085 (%)
Female	239 (62.7)	142 (37.3)	381 (35.12)
Male Civilian/soldier status	449 (63.8)	255 (36.2)	704 (64.9)
Civilian	474 (61.4)	298 (38.6)	772 (71.2)
Demographics	Pre- PHEIC, *n* (%)	Post- PHEIC, *n* (%)	Total population, N = 1,085 (%)
Soldier/retired soldier	214 (68.4)	99 (31.6)	313 (28.8)
Age*			
0–17	125 (74.9)	42 (25.1)	167 (15.4)
18–24	68 (61.2)	45 (39.8)	113 (10.4)
25–34	152 (63.9)	86 (36.1)	238 (21.9)
35–44	162 (63.3)	94 (36.7)	256 (23.6)
45–54	94 (63.5)	54 (36.5)	148 (13.6)
55–64	43 (51.8)	40 (48.2)	83 (7.6)
65–74	23 (50.0)	23 (50.0)	46 (4.2)
≥ 75 HIV coinfection	21 (61.8)	13 (38.2)	34 (3.1)
Positive	176 (60.7)	114 (39.3)	290 (26.7)
Negative	444 (65.4)	235 (34.6)	679 (62.6)
Not tested TB type	68 (58.6)	48 (41.4)	116 (10.7)
Active	307 (55.5)	246 (44.5)	553 (51)
Latent	381 (71.6)	151 (28.4)	532 (49)

*PHEIC = Public Health Emergency of International Concern; TB = tuberculosis. *Percentages do not equal 100% due to rounding.*

b) Pearson's chi-Squared Tests

We conducted a series of three Pearson's χ^2 tests to test the null hypothesis that there was no association between pre- and post-PHEIC status and TB treatment outcome (Table 2). When pre- and post-PHEIC status was determined as before or after August 8, 2014, and all patients were included, the test showed that there was a difference in treatment outcomes between pre- and post-PHEIC status patients (χ^2 = 16.25, P = 0.001) (Table (Table3). Additionally, when pre- and post-PHEIC status was determined including all patients with active TB, the test showed that there was a difference in treatment outcomes between pre- and post-PHEIC status patients (χ^2 = 21.04, P < 0.001). However, there was no statistically significant difference between treatment outcomes determined between pre- and post-PHEIC status of patients with latent TB (χ^2 = 1.6215, P = 0.66).

Table 2: Summary of Tb Treatment Outcomes of Patients (N = 1,085) t 34 Military Hospital in Freetown, Sierra Leone, from 2012 To 2016

Outcome	Pre-PHEIC, *n* (%) Post-PHEIC, *n* (%) Total, *n*		
Cured	85 (37.1)	144 (62.9)	229
Completed	174 (36.1)	308 (63.9)	482
Abscond	0 (0)	1 (100)	1
Default	47 (28.1)	120 (71.9)	167
Lost to follow-up	0 (0)	7 (100)	7
Transferred	10 (28.6)	25 (71.4)	35
Unknown	45 (60)	30 (40)	75
Failed	2 (100)	0 (0)	2
Died	34 (39.1)	53 (60.9)	87

*PHEIC = Public Health Emergency of International Concern; TB = tuberculosis. *Percentages are reported as percentage of all patients in each category.*

Table 3: Results from Pearson's Chi-Square Tests, Including Expected and Observed Proportions for Each Treatment Outcome, before and After the Pheic Declaration on August 8, 2014

	Treatment outcome			
Time	Successful	Lost to follow-up	Unknown	Unsuccessful
	Expected proportions, all patients* (χ^2 = 16.25, P = 0.001)*			
Pre-PHEIC	0.24	0.06	0.04	0.03
Post-PHEIC	0.42	0.10	0.06	0.05
	Observed proportions, all patients*			
Pre-PHEIC	0.24	0.04	0.05	0.03
Post-PHEIC	0.42	0.12	0.05	0.05
	Expected proportions, active TB patients (χ^2 = 21.038, P < 0.001)*			
Pre-PHEIC	0.32	0.05	0.05	0.03
Post-PHEIC	0.40	0.06	0.06	0.04
	Observed proportions, active TB patients			
	Treatment outcome			
Time	Successful	Lost to follow-up	Unknown	Unsuccessful
Pre-PHEIC	0.32	0.03	0.07	0.03
Post-PHEIC	0.41	0.08	0.03	0.03
	Expected proportions, latent TB patients (χ^2 = 1.6215, P = 0.6545)			
Pre-PHEIC	0.17	0.06	0.03	0.03
Post-PHEIC	0.42	0.16	0.07	0.07
	Observed proportions, latent TB patients			
Pre-PHEIC	0.16	0.06	0.03	0.03
Post-PHEIC	0.43	0.16	0.07	0.07

*PHEIC = Public Health Emergency of International Concern; TB = tuberculosis. *Indicates significant differences (P < 0.05) in treatment outcomes between groups.*

c) Regression Analyses

A series of multinomial logistic regressions were calculated to test the probabilities of treatment outcomes based on patient characteristics and the number of months since the EVD outbreak. The model selection process showed that the optimal model included TB type, the number of months after the EVD outbreak, HIV status, age, and an interaction between age and HIV status (Supplemental Table 1). Calculation of the Akaike weight showed that this model had a 67% chance of being the optimal model for the data, and no other model fell within a ΔAIC of 2 points of the optimal model. Full reporting of odds ratios and 95% confidence intervals (CIs) calculated from the coefficients of the optimal model can be found in Table 4. Overall, regression results showed that, regardless of HIV status, as the number of months since the EVD outbreak increased, the probability of a successful treatment outcome occurring declined whereas the probability of an unknown or unsuccessful outcome increased (Figure 1). The odds of an unknown outcome and unsuccessful outcome were 1.179 (95% CI: 1.157–1.203) and 1.034 (95% CI: 1.007–1.0623) more likely than a successful outcome, respectively, for each progressive month after the PHEIC was declared (Table 4). The probability of the treatment outcome of lost to follow-up or unsuccessful declined as the number of months since the EVD outbreak also increased, regardless of HIV status.

Table 4: Odds Ratios and 95% Confidence Intervals (CIs) of Optimal Multinomial Logistic Regression Model, using Successful as Reference Treatment Outcome, HIV-Negative Status as Reference Covariate for HIV Status, and Active TB as Reference Covariate for Type TB

Covariate	Lost to follow-up Successful (95% CI)		Unknown (95% CI)	Unsuccessful (95% CI)
Intercept	–	0.087 (0.052–0.144)*	0.03 (0.017–0.055)*	0.008 (0.003–0.02)*
Months after outbreak	–	0.953 (0.922–0.984)*	1.179 (1.157–1.203)*	1.034 (1.007–1.062)*
Age	–	1.018 (1.007–1.029)*	1.014 (1.002–1.026)*	1.044 (1.026–1.063)*
HIV negative	–	–	–	–
HIV not tested	–	1.175 (0.442–3.125)	3.291 (1.179–9.184)*	5.095 (1.103–23.534)*
HIV-positive	–	3.852 (1.262–11.756)*	1.48 (0.414–5.29)	11.942 (2.969–48.028)*
Active TB	–	–	–	–
Latent TB	–	2.029 (1.421–2.898)*	1.612 (1.112–2.338)*	1.662 (1.057–2.615)*
Age × HIV negative	–	–	–	–
Age × HIV not tested	–	1.021 (0.998–1.044)	0.987 (0.96–1.015)	0.996 (0.966–1.028)
Age × HIV positive	–	0.967 (0.938–0.996)*	0.981 (0.95–1.012)	0.973 (0.943–1.003)

**Represents a statistically significant odds ratio (P < 0.05) indicating an association between the covariate and outcome, using a 95% CI.*

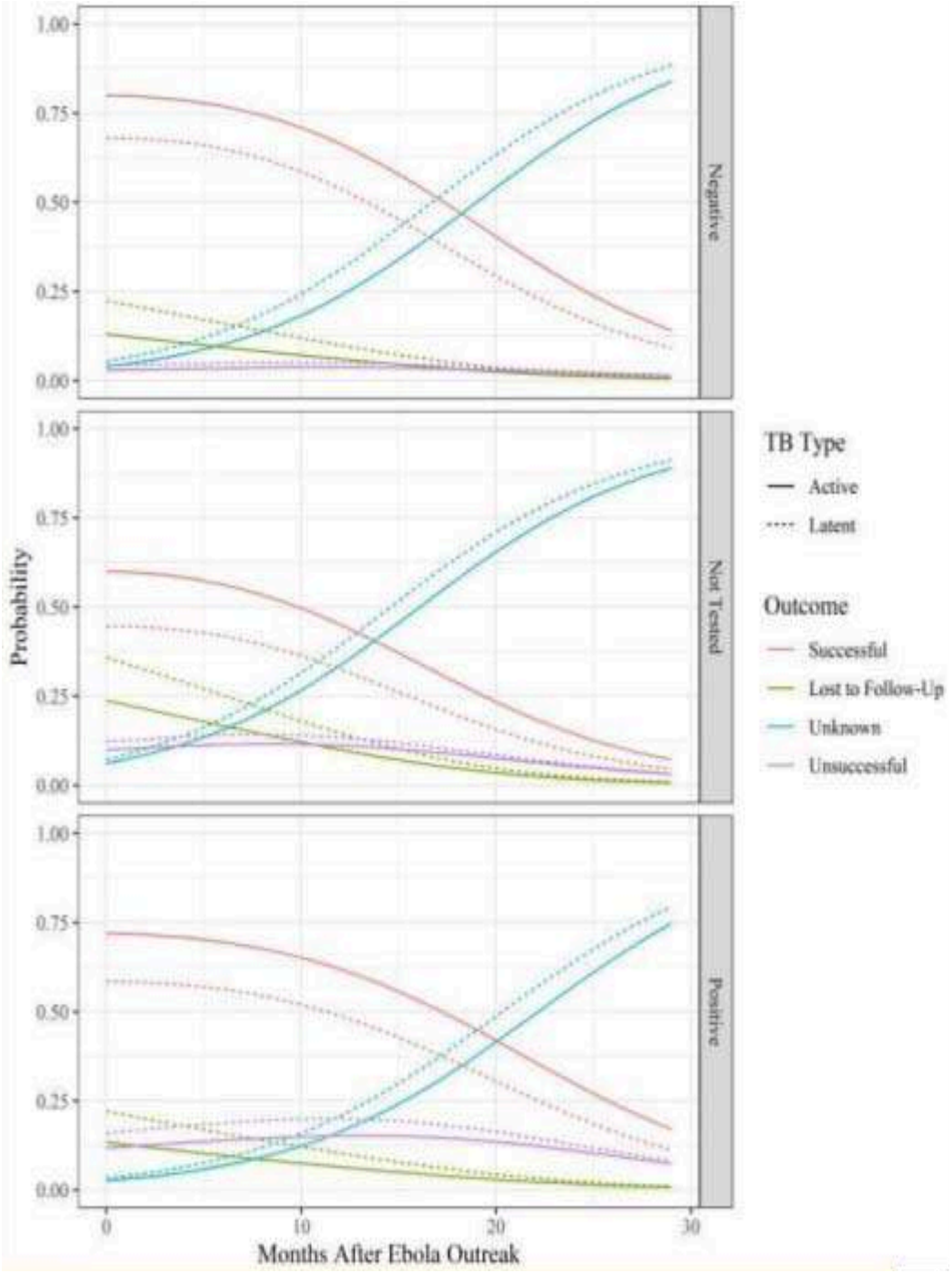

Figure 1: Predicted Tuberculosis (TB) outcomes as Ebola Outbreak Progresses. Predicted Probabilities based on Optimal Multinomial Logistic Regression Model of the Influence of HIV Status, TB type, Patient age, and time Since the EVD Outbreak on TB Treatment Outcome for Patients in 34 Military Hospital in Freetown, Sierra Leone, from 2012 to 2016. This Figure Appears in Color at *www.ajtmh.org*.

HIV status had a significant impact on TB treatment outcomes. Overall, HIV-positive patients had a slightly lower probability of successful treatment and a slightly higher probability of an unsuccessful treatment than HIV negative patients throughout the study

period. Patients that had unknown HIV status had the lowest probability of a successful outcome and the highest probability of an unknown outcome (Figure 1). Using HIV-negative status and successful outcomes as reference categories, HIV-positive patients were more likely to be lost to follow-up or have an unsuccessful treatment outcome (Table 4).

TB status also had a significant impact on treatment outcomes. Regardless of HIV status or the number of months after the EVD outbreak, patients with active TB had a higher probability of a successful treatment outcome and a lower probability of an unsuccessful or unknown outcome or being lost to follow-up. Odds ratios for TB status showed that the odds of a patient with latent TB being lost to follow-up were 2.029 times higher (95% CI: 1.421–2.898) than the odds of a patient with active TB being lost to follow-up. Similarly, the odds of a patient with latent TB having an unknown treatment status or an unsuccessful treatment were 1.612 (95% CI: 1.112–2.338) and 1.662 (95% CI: 1.057–2.615) times higher than active TB patients, respectively. Age of the patient and the interaction between age and HIV status were also included in the optimal model. In general, as patient age increased the probability of a successful outcome decreased (Figure 2). Before the EVD outbreak, as age increased for HIV-positive patients, the probability of an unsuccessful treatment outcome increased, the probability of being lost to follow-up decreased, and the probability of successful or unknown outcomes stayed nearly the same (Figure 2). Alternatively, as age increased in patients who were not tested or tested negative for HIV, the probability of being lost to follow-up increased, and the probability of successful outcomes decreased. Although these same age-related trends occurred after the EVD outbreak, as time passed, the probability of an unknown outcome increased and the probability of a successful outcome decreased, regardless of HIV status or age.

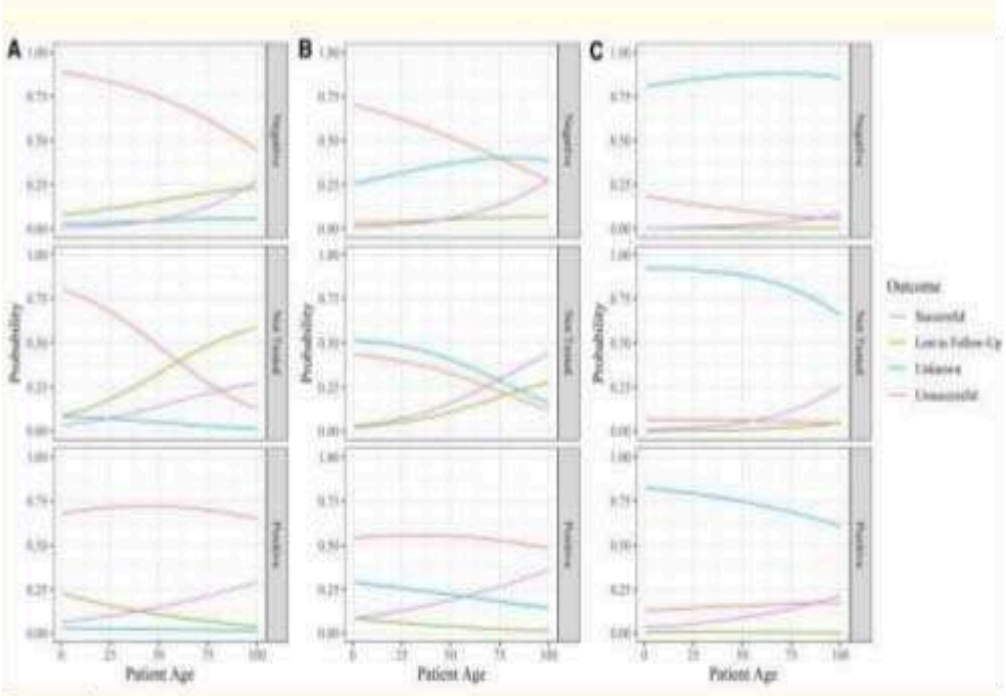

Figure 2: Probability of Tuberculosis (TB) Outcomes by age, Compared Across 15-Month Intervals. Multinomial Logistic Regression of TB Outcomes by HIV Status after the Ebola Virus (EVD) Outbreak by Patient age (0–100 years), at Time (A) 0 months, (B) 15 months after Outbreak, and (C) 30 months after Outbreak for Patients in 34 Military Hospital in Freetown, Sierra Leone, from 2012 to 2016. This Figure Appears in Color at *www.ajtmh.org*

IV. DISCUSSION

Overall, this retrospective analysis of data from the 34 Military Hospital in Freetown, Sierra Leone, on TB treatment outcomes before and after the 2014 EBV outbreak showed that there were significant differences in treatment outcomes before and after the EVD outbreak. Regression results showed that treatment outcomes were influenced by the length of time passed since the EVD outbreak declaration, HIV and TB status, and patient demographics. The declines in the probability of an outcome being successful, unsuccessful, or lost to follow-up as the EVD outbreak continued was likely due to the vast increase in the number of cases with unknown outcomes. This supports the hypothesis that patients who were previously being seen for TB infections and/or TB/HIV coinfections may have stopped visiting the hospital either because of fear of infection with EVD and/or the discontinuation of treatment programs. Ansumana et al. (2017) similarly described widespread avoidance of healthcare in Sierra Leone during the Ebola epidemic, where current HIV and TB patients discharged themselves and prospective patients did not seek treatment at all.[3] A similar study examining HIV during the EVD epidemic described the effects of the Ebola epidemic on HIV treatment of soldiers in Sierra Leone and found that there was a much greater risk of patients being lost to follow-up, defaulting, and going without treatment. [24] A study done by Parpia et al. (2016) modeled the effects of treatment coverage reduction caused by the Ebola epidemic in Sierra Leone on deaths related to HIV, TB, and malaria predicted that a 50% reduction in treatment coverage reported for Sierra Leone would cause more than 2,500 indirect deaths.[4] A 65% reduction in treatment coverage was predicted to cause equal numbers of direct deaths from Ebola and indirect deaths from HIV, TB, and malaria.[4] Taken in this context, the vast increase in unknown treatment outcomes shown in this study not only highlights the interruption in access to healthcare, but it also suggests the possibility that many of those unknown treatment outcomes were unsuccessful TB outcomes as the Ebola epidemic continued. This study also highlights the need for improved efforts to track patients during future treatment interruptions.

The results presented here conflict with those reported by Bah et al. (2017), who reported an increase in the number of successful treatment outcomes of TB patients during the Ebola epidemic in the Bombali District of Sierra Leone.[2] These increased successful outcomes were attributed to greater accessibility to healthcare as vast resources were deployed in Sierra Leone.[2] Additionally, this study used a different threshold for the beginning of the Ebola period, beginning the EVD outbreak on June 1, 2014, versus August 8, 2014, used in this analysis.[2,18] Alternatively, these results were based on a smaller sample size for treatment outcome comparisons (n = 226) and used only χ^2 tests for comparisons.[2] Our results suggest that other factors influenced treatment outcome, particularly age and HIV status.[2] Therefore, differences in demographics between this study and that done by Bah et al. (2017), or the fact that they were not factored into their analysis, may explain the difference in treatment outcome results.

Ortuno-Gutierrez et al. (2016) also reported different results within Guinea, in line with those reported by Bah et al. (2017), where contingency planning and increased health support resulted in slightly higher TB treatment success rates. [25] The regression results showed that HIV status, age, and TB status had an influence on TB treatment outcomes. Overall, HIV-positive patients had lower probabilities of successful outcomes and higher probabilities of unsuccessful treatment outcomes in comparison to HIV negative patients. These results are in line with results reported by Tweya et al. (2013) and Kliiman and Altraja (2009), who reported that HIV coinfection was associated with poorer treatment outcomes.[26,27]

Older patients in this study consistently had higher probabilities of poor treatment outcomes compared with younger patients, which is not surprising given the well-described negative effect of age on TB treatment outcomes described in other studies.[28] Patients with active tuberculosis had higher probabilities of successful treatment

outcomes than patients with latent tuberculosis. This difference in treatment outcomes is likely due to the nature of active TB, where patients who are experiencing symptoms are more likely to seek treatment for TB and therefore more likely to have a successful outcome.[29]

Several studies have evaluated the indirect impacts of the EVD outbreak on healthcare services for diseases that require regular care, such as TB, HIV, and malaria.[3,4,7] It is also well understood that sporadic interruptions to TB and HIV treatment can increase the risk of poor treatment outcomes, opportunistic infections, and death by any cause.[30] The timing of this impact has also been studied, and evidence of decreased testing and treatment of TB and HIV, as well as poor treatment outcomes among those with TB and HIV, correlated with the peak of the EVD outbreak.[31]

V. LIMITATIONS

This study was limited in that it assumed a constant level of impact on TB outcomes throughout the EVD outbreak after the PHEIC declaration, without accounting for fluctuations in disease incidence and societal disruptions in the region. This simplification, not accounting for changes in rate of new infections over time in the model, simplifies the model to an extent. Furthermore, by using a military hospital, this study captures both military and civilian populations, which may not be representative of the general population of Freetown. Finally, this study is exposed to many of the general weaknesses inherent in examining retrospective clinical data, such as missing patient data, potential misrepresentation of the general population due to a limited sample, limited measures of other risk factors that may be important to treatment outcomes, and potential for misclassification of diagnoses. Another limitation of this retrospective dataset was a lack of clearly defined diagnosis criteria for active and latent TB and no specification of drug types used for treatment.

VI. CONCLUSIONS

TB treatment outcomes were shown to be influenced by the length of time that had passed since the EVD outbreak declaration, patient age, whether patients had active or latent TB, and their HIV infection status. Most notably was the change in the proportion of patients with treatment outcome categorized as successful, unsuccessful, or lost to follow-up shifting to unknown as the outbreak progressed. These results identify patients who are most at risk for unsuccessful TB treatment outcomes based on the factors indicated earlier during different points in the timeline after a disturbance. Because 34 Military Hospital is currently the main referral hospital for Sierra Leone's severe COVID-19 cases, further studies on the impact shifting resources, interruptions to care, and decreased treatment seeking on TB outcomes could further inform our understanding of whether these disturbances are uniform in their impact on TB treatment outcomes.

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