Cardiovascular Mortality in Brazil during the COVID-19 Pandemic: a Comparison between Underlying and Multiple Causes of Death

Abstract

Introduction: The Covid-19 pandemic has differentially impacted cardiovascular disease (CVD) mortality worldwide. Causes of death misclassification may be one of the reasons. We evaluated the impact of the pandemic on CVD mortality in Brazil, comparing underlying (UC) and multiple causes (MC) of death.

Methods: Ecological, time series study analysing age-standardized death rates for CVD, from epidemiological week 10/2020 to 39/2021, using data from the Mortality Information System, Brazil. CVD was defined using ICD-10 coding, if reported as UC or MC of death. Observed and expected data (mean for the same EW, 2017–2019) were compared. Risk ratios (RiR) were analysed and 95% confidence intervals (CI) were calculated.

Results: Age-standardized mortality rate for CVD as UC of death was 165.8 (95%CI 165.4-166.3)/100,000 inhabitants, similar to expected (165.6/100,000, 95%CI 165.2-166.1, RiR=1.00). There was increased out-of-hospital mortality (RiR=1.18; 95%CI 1.17-1.19) and deaths of ill-defined causes (RiR=1.43; 95%CI 1.42-1.44). The increase in out-of-hospital deaths was more pronounced in the North (RiR=1.33; 95%CI 1.30-1.36), region with less resilient health system. Conversely, as MC of death, there was a 10% increase in CVD mortality (observed: 243.2 (CI95% 242.7-243.7), expected: 221.6 (95%CI 221.1 – 222.1)/100,000). An increase also occurred in the North and Central West regions (RiR=1.16; 95%CI 1.15-1.18), among men (RiR=1.11; 95%CI 1.11-1.12) and individuals ≥60 years (RiR=1.11; 95%CI 1.10-1.11).

Conclusions: During the pandemic, mortality rates for CVD as MC of death increased in Brazil, whereas as UC mortality rates did not change. Higher out-of-hospital mortality, misclassification, and competing causes of death may explain this pattern.

Keywords: *Covid-19, cardiovascular diseases, mortality, multimorbidity, Brazil*

Introduction:

The impact of the Covid-19 pandemic on cardiovascular disease (CVD) mortality has been substantial.[1] While some countries reported excess CVD deaths during the pandemic, others did not, although more deaths consistently occurred out of hospitals.[2-4] In Brazil, there was an excess of CVD deaths in five out of six Brazilian state capital cities, concomitantly with an increase in home deaths.[5] This increase in mortality occurred in parallel with a reduction in CVD hospitalizations, however with a higher proportion of intensive care use and in-hospital mortality, suggesting greater clinical severity or compromised care.[6-8] However, even though this pattern of changes in hospitalizations was observed in another Brazilian state capital city, a parallel increase in CVD mortality was not found.[9]

The heterogeneity of the Covid-19 pandemic effect in CVD mortality according to locations may be due to differences in the direct, indirect, and long term effects of the pandemic.[10] Importantly, misclassification of the underlying cause (UC) of death may also play a role, particularly considering that more deaths occurred at homes with impaired access to diagnosis.[1]

In this context, the analysis of UC of death may be an oversimplification of the morbid process, particularly in the presence of multimorbidity.[11] Multiple causes (MC) of death analysis is an appropriate complementary methodology that examines any mention of a disease in the death certificate (DC). This methodology is particularly informative in situations with a greater complexity of the morbid process, in addition to uncertainty about the quality of mortality information, such as during the pandemic.[12-14] This study aims to evaluate impact of the Covid-19 pandemic on CVD mortality in Brazil in 2020 and 2021, comparing UC and MC of death.

Methods:

Study design, location, period and data sources:

This is an ecological, time series study, in which vital statistics data from the Mortality Information System (SIM) for Brazil and its 5 geographical regions were analyzed from epidemiological week (EW) 10/2020 (March 1st to 7th) – after the first Covid-19 case was confirmed in Brazil in February 26th – to EW 39/2021 (September 26th to October 2nd). Data extraction was finalized in March 2022. More details about SIM is in **Supplementary Methods 1**. The geographical regions are North, Northeast, Central West, Southeast, and South (the North and Northeast being the least developed).[15] Details about the Brazilian health system have been previously published.[15]

Definitions of CVD:

For the analysis of UC of death, cardiovascular causes reported in the last completed line of DC's first part were considered and defined according to the ICD-10, chapter IX, as detailed in **Supplementary Methods 2**. Chapter XVII, of congenital heart disease, was also included. Covid-19 deaths were defined as ICD-10 B342.[16,17] Ill-defined causes of death were defined as: unknown or unspecific causes (ICD-10 R95 to 99) and signs and symptoms related to the circulatory and respiratory systems (ICD-10 R00 to R09) from ICD-10 chapter XVIII, in addition to code I46 (cardiopulmonary arrest). These were all considered as "*garbage*" codes and were used as a proxy to evaluate quality of death records.

Multiple causes of death:

For the analysis of MC of death, all causes reported in any line of the DC's part V were considered (lines A to D; II). As such, MC of death is the sum of UC and associated causes. For definition of associated cause of death, we considered the same ICD-10 codes for the UC, when they were present in any line of DC, except in the line corresponding to the UC.[18] There were only two exceptions of CVD ICD-10 codes that were only considered if reported as UC of death: a) ICD-10 code I46 (cardiorespiratory arrest), considered as cardiovascular cause when reported as UC, but excluded from the analysis when informed as associated cause, because it can be the final mechanism of death of several diseases; b) ICD-10 code I10.0 (primary hypertension) considered only when reported as UC, but not as AC, because hypertension is a highly prevalent risk factor in Brazil (32% of the adult population)[19], and frequently reported as an associated condition of deaths We made this decision to allow better interpretation of MC of death data, as the high numbers of ICD 10 code I10 reported as MC of death in previous years and the greater rise in 2020 compared to 2019 could make the interpretation of the MC of death analysis difficult. (**Supplementary Methods 3**)

Definitions of indicators:

Three indicators were evaluated for mortality: mortality rate, out-of-hospital mortality rate and proportion of out-of-hospital deaths, for both analysis of UC and MC of death. Age-standardized rates were presented, based on age distribution of the Brazilian population estimated for 2020, considering a 5-year interval. The denominator to calculate rates was the population based on by Ministry of Health estimates at municipal level for 2020, aggregated for Brazil and regions.[20]

Subgroup and sensitivity analyses:

The three aforementioned indicators were stratified into subgroups according to: sex, age (<30, 30-59, ≥60 years); and human development index (HDI, a marker of socioeconomic development ranging from 0 to 1, being 1 the highest development).[21] Brazilian municipalities were stratified by HDI into terciles, considering the distribution of each region. An additional analysis was carried out for types of CVD [acute coronary syndromes (ACS), stroke and heart failure (HF) plus cardiomyopathies]. Finally, analysis of MC of death was carried out separately for the subgroup in which Covid-19 was the UC, as well as for cases in which the UC was different from CVD or Covid-19, to evaluate whether the potential change in CVD as MC of death also occurred in deaths not classified as due to Covid-19.

Statistical analysis:

Observed mortality data were compared to expected, defined as the average of the previous three years (2017-2019) by EW. Absolute differences and risk ratios (RiR) were calculated for each group according to cause of death, characteristics of the individual and municipality, region of the country and phase of the pandemic. RiR was calculated by dividing observed values by expected values for each period, and 95% confidence intervals (CI) were estimated by standard errors (SE), based on the delta method. For proportions, CI were estimated based on the normal approximation to the binomial distribution. For time series analyses, the 5-week moving average of the indicators evaluated in the pandemic were compared with the 5-week moving average of the reference period (2017 to 2019). The maximum and minimum values for a given EW were used as measures of dispersion. Statistical analyses were performed using the “R” software (The R Foundation for Statistical Computing, Vienna, Austria), version 4.0.1.

Ethical Considerations and data availability:

The analyses were carried out in public and unidentified databases, available at https://datasus.saude.gov.br/transferencia-de-arquivos/. The steps to access data are described in **Supplementary Methods 1**.

Results:

CVD as underlying causes of death

During the study period, the age-standardized CVD mortality rate for UC of death was similar to the expected rate (RiR 1.00, 1.00-0.93) (**Table 1**). There was an increase in CVD mortality in the beginning of the pandemic followed by a decrease corresponding to the 1st peak of the pandemic in Brazil and by a subsequent increase during the 2nd peak of the pandemic, when deaths from Covid-19 were the highest (**Figures 1-A and 1-B**).

Different from the stable pattern observed for overall CVD mortality, there was an increase in the out-of-hospital mortality rate (RiR: 1.18; 1.17-1.19), and a substantial increase in the proportion of out-of-hospital deaths [RiR: 1.18 (1.18-1.18)] (**Table 1**). The out-of-hospital mortality had a different pattern from total CVD mortality, since two well defined peaks were observed, remaining above the historical series during the whole period (**Figure 2**). The increase in out-of-hospital CVD mortality was paralleled by a 43% increase in ill-defined causes with RiR: 1.43 (1.42-1.44). Among out-of-hospital deaths, the increase of ill-defined causes was even more significant [RiR: 1.51 (1.50-1.53)] (**Table 2**).

Regional trends for CVD as underlying causes of death

Although there was a stability in CVD age-standardized mortality as UC in the country, regionally there was a significant increase in these rates in the North and Central West regions, while a borderline decrease was observed in the Southeast (**Table 1**), the most populous region of the country. Regarding out-of-hospital death rates, the increase was again more pronounced in the North (RiR: 1.33; 1.30-1.36) and Central-West (RiR: 1.26; 1.23–1.30). The peak of out-of-hospital CVD mortality, concomitantly with the 1st peak of Covid-19, suggests the occurence of competing demands for hospital beds, as observed in the North and Northeast (**Figure S1**)[7].

CVD as multiple causes of death

During the pandemic, there was an increase in the number of causes of death reported in the DC (**Figure S2**). Considering CVD as MC of death, there was an increase in age-standardized mortality rates of 10% and also in the absolute number of deaths (**Table 1, Figure 3-A)**. This increase contrasts with the stable trend observed in the UC of death analysis (**Table 1)**. Compared to the UC time series analysis, there were 2 better-defined peaks of CVD mortality as associated causes of death, in the beginning of the pandemic and concurrent with the 2nd peak of hospitalization in all Brazilian regions (**Figure S3**). Also, the increase in CVD mortality as MC of death was associated with the reports of CVD as AC in patients who died of Covid-19 as UC, with near-superimposable curves (**Figure S4**).

Regarding out-of-hospital deaths, there was a similar increase in mortality rates when CVD were considered as MC (RiR: 1.19, 1.18–1.20), compared to UC (18%). (**Table 1, Figure 3-B**).

Regional trends for CVD as multiple causes of death

The increase in CVD death rates as MC of death was more pronounced in North (RiR: 1.16 (1.15–1.17)), and Central West (RiR: 1.16 (1.15–1.18)) regions (**Table 1**). For out-of-hospital mortality rates, steeper increases were also observed in the North (RiR: 1.35 (1.32–1.38)) and Central West (RiR: 1.27 (95% CI 1.24–1.30)) regions, followed by the Northeast (RiR: 1.19 (1.18–1.20)], reinforcing the regional trends, presumably associated with the lower resilience of local health systems (**Table 1**).

Mortality from CVD as multiple causes – subgroup and sensitivity analyses

In subgroup analyses (HDI strata, age group and sex), there was a greater increase in CVD mortality as MC in older individuals [60 years and over, RiR: 1.11 (1.10-1.11)], compared to those younger than 30 years [RiR: 0.91 (0.89–0.93)], and to individuals aged 30 to 60 years (RiR: 1.07 (1.06–1.08)) (**Supplementary Table 1).** In addition, men had a greater increase in mortality [RiR: 1.11 (1.11–1.12)] compared to women [RiR: 1.08 (95% CI 1.08-1.09)]. No significant difference was observed for the HDI strata (**Supplementary Table 1**).

Regarding CVD specific causes of death, a more significant increase was observed for stroke rates as MC (RiR: 1.10 (1.09 – 1.10)), considerably higher than the RiR for HF/cardiomyopathies (RiR: 1.05 (1.05–1.06) and ACS (RiR: 1.03 (1.02–1.03) (**Supplementary Table 2**). These findings contrast with the analysis of CVD as UC in which a significant increase was observed only for arrhythmias (RiR: 1.22 (1.19–1.24)), which includes the unspecific code for cardiac arrest (I46), and thus could result from misclassification, and hypertension (RiR: 1.50 (1.48–1.52), with a stable or downward trend for the other CVD causes (**Supplementary Table 2).**

Discussion

In this analysis of the impact of the Covid-19 pandemic on CVD mortality in Brazil during EW 10/2020 to 39/2021, we observed an increase in CVD mortality for MC of death, contrasting with a stable pattern for CVD deaths when the usual analysis of UC was undertaken. This increase occurred in parallel with rises in out-of-hospital and ill-defined causes of deaths in the country, and were observed particularly for deaths for which the UC was Covid-19. Moreover, the increase in CVD as MC of death was more pronounced in the North and Central West regions, where poorer health system resilience has been recognized.[22,23] Taken together, our nationwide analysis comparing UC and MC of death analysis innovates and complements previous approaches focusing on UC of death, helping to elucidate interactions between Covid-19 and CVD.

Our findings reinforce that the effect of the pandemic on CVD mortality is multifaceted and results from direct and indirect effects, such as: 1) reduced access to healthcare due to mitigation policies or health system issues, corroborated by the rise in out-of-hospital deaths,[5,9,22] 2) worsening quality of vital statistics data, due to less access to specific diagnosis or overwhelmed health systems, revealed by the increase in ill-defined deaths[24], and 3) competing causes of death between Covid-19 and CVD, in which individuals with prevalent CVD may have had an anticipated death due to Covid-19, considering the documented greater severity of Covid-19 in these individuals,[25] and suggested by the rise in CVD as AC of death for individuals that had Covid-19 as the UC of mortality.

While previous literature, has shown a consistent reduction in hospitalizations from CVD during the pandemic,[6,8] and a displacement of deaths to the out-of-hospital setting,[5,9] the effects on population-level CVD mortality were more heterogeneous: some countries showed a stability or decrease,[4,26] while others, such as England, the US and China showed an increase in CVD deaths.[1] A heterogeneity across countries may indeed be possible considering the differences in number of Covid-19 cases, health system characteristics, age structure of populations, and prevalence of CVD and their risk factors.[1] However, considering that a pronounced reduction in hospitalizations for CVD which require in-hospital treatment for mortality reduction (such as ACS)[27] were observed in Brazil, with higher proportional in-hospital mortality,[6] a reduction in CVD mortality, as observed in our UC of death analysis was counterintuitive. In addition, because it may be difficult to differentiate between Covid-19 and CVD in a sudden death or respiratory failure context, particularly in a scenario of multimorbidity and impaired access to care – such as out-of-hospital – misclassification of the UC of death had to be considered.[1,24]

In this context, the MC of deaths analysis herein depicted confirms our hypothesis by showing a rising pattern in CVD as associated causes of death, revealing the uncertainty about causes of death during a health crisis. Of note, the rise in CVD as MC was clearly related to the deaths reported to be due to Covid-19, emphasizing the potential interaction of both. This interaction may result from the direct effect of SARS-COV2 to the cardiovascular system, but also to indirect effects, which may be more systemic, and location-dependent.[25] In Brazil, more vulnerable individuals have higher CVD prevalence and are also more prone to be infected by SARS-COV2, as they are more exposed to the virus due to living and working conditions and, ultimately, impossibility to adhere to social isolation measures.[22,23,28] Moreover, these same individuals had more excess deaths during the pandemic, possibly because of multimorbidities or more impaired access to healthcare.[28,29]

Our subgroup analysis corroborates the importance of health vulnerability as one of the factors that drove the increase in CVD mortality. The greater negative effects on mortality rates were observed in the least developed regions of Brazil, where healthcare infrastructure is more fragile,[22] even though changes in mortality rate was not related to HDI. From the individual's perspective, those who had a presumably higher cardiovascular risk (older and men) were also more negatively impacted. These findings, allied with previously published data from Brazil that revealed greater excess of deaths among black individuals and those living in areas with higher vulnerability,[28,29] support the value of addressing social determinants to confront health disparities, particularly exacerbated during a pandemic.

Regarding the effect of the pandemic's phase on CVD deaths, there was a small increase in CVD deaths as UC at the beginning of the pandemic probably related to misclassification of Covid-19 deaths as CVD, and then a decline, when CVD deaths may have been misclassified as Covid-19, as a result of impaired access to diagnosis. Later on, concurrent with the peak of Covid-19 deaths in 2021, there was a second rise in the number of total and out-of-hospital CVD deaths, when overwhelmed hospitals may have played a role. Importantly, when evaluating UC of death analysis temporal trends, the reduction in CVD mortality is concurrent with the rise in out-of-hospital deaths, raising concern for misclassification. The MC of death temporal trend analysis is complementary, showing that the CVD mortality changes occurred in parallel with the Covid-19 death curves, suggesting a component of competing causes in the context of multimorbidity.

For subtypes of CVD in MC of death analysis, the more significant increase occurred for stroke, finding that could be related to the easiest identification of stroke as an independent diagnosis of Covid-19, due to different symptoms, compared to ACS and HF.[30] Only arrhythmia and hypertension had an increase in mortality rate as UC, a finding that must be misleading as they include garbage codes, such as cardiac arrest (I46).

The limitations of the present analysis relates to the limitations of national vital statistics database, which is internationally well rated for quality,[31] but has not been completely qualified at the time of the present analysis. However, the consolidated database will only be publicly available two years after the calendar year. Moreover, the data quality is heterogeneous across regions, and comparisons between regions should be made with caution. Another limitation is the decision to exclude ICD codes for hypertension in the MC of death analysis, which may have caused bias. Lastly, the changes in CVD mortality may also result from a reduction in the incidence of CVD, which was not taken into account in the present analysis due to lack of data in Brazil. However, although some studies report possible causes for a decrease in CVD incidence during the pandemic, such as reduction in air pollution,[32] others confront that showing an increase in unhealthy habits, such as smoking and stress, and lower access to healthcare.[33,34]

Taken together, the MC of death approach complemented the analysis of the impact of the Covid-19 pandemic on CVD mortality in Brazil, bringing different and powerful insights into the changes in CVD mortality during this period, and reflecting the multifaceted interaction of Covid-19 and CVD in the morbid process. This analysis also emphasises the importance of vital statistics data quality, and how the negative impacts of the pandemic on CVD are intertwined with health system resilience, suggesting that investing in the preparedness of more vulnerable local health systems is a potent tool to mitigate the impacts of a health crisis.

Conclusions:

During the Covid-19 pandemic, there was a marked increase in CVD mortality as MC, while deaths due to CVD as UC remained stable in Brazil, revealing the complementary importance of MC of death analysis to better understand the interaction of Covid-19 and CVD. Higher out-of-hospital mortality, misclassification, and competing causes of death may have contributed to this pattern.

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Figures legends:

Figure 1: A: Number of observed cardiovascular deaths in Brazil from 2017 to 2021 (red line), compared to the mean number of cardiovascular deaths from 2017 to 2019 per epidemiological week (dotted line), considering underlying causes of death. B: Number of observed cardiovascular (blue line) and Covid-19 (red line) deaths in Brazil, from 2017 to 2021, compared to the mean number of cardiovascular deaths from 2017 to 2019 per epidemiological week (dotted line), considering underlying causes of death.

Figure 2: Number of out-of-hospital cardiovascular deaths in Brazil, from 2017 to 2021 (red line), compared to the mean number of out-of-hospital cardiovascular deaths from 2017 to 2019 per epidemiological week (dotted line), considering underlying causes of death.

Figure 3: A: Number of observed cardiovascular deaths in Brazil from 2017 to 2021 (red line), compared to the mean number of cardiovascular deaths from 2017 to 2019 per epidemiological week (dotted line), considering multiple causes of death. B: Number of observed out-of-hospital cardiovascular deaths in Brazil from 2017 to 2021 (red line), compared to the mean number of cardiovascular deaths from 2017 to 2019 per epidemiological week (dotted line), considering multiple causes of death.

Table 1: Observed and expected age-standardized mortality rate (for 100,000 inhabitants) and risk ratios for cardiovascular diseases as underlying and multiple causes of death in Brazil and regions, epidemiological weeks 10/2020-39/2021.

Cardiovascular Disease Standardized Mortality Rate (100k inhabitants), Epidemiological Weeks (10/2020-39/2021), Brazil and Regions						
	Underlying causes of death:			**Multiple causes of death:**		
	Observed (CI 95%)	**Expected (CI 95%)**	**Risk Ratio (CI 95%)**	**Observed (CI 95%)**	**Expected (CI 95%)**	**Risk Ratio (CI 95%)**
Brazil						
Mortality Rate	165.9 (165.47;166.34)	165.62 (165.18;166.06)	1.00 (1.00;1.01)	243.18 (242.65;243.71)	221.62 (221.12;222.13)	1.10 (1.09;1.10)
Out-of-hospital Mortality Rate	51.05 (50.81;51.29)	43.26 (43.04;43.48)	1.18 (1.17;1.19)	63.2 (62.93;63.47)	53.04 (52.8;53.29)	1.19 (1.18;1.20)
% Deaths at Home	0.31 (0.31;0.31)	0.26 (0.26;0.26)	1.18 (1.18;1.18)	0.26 (0.26;0.26)	0.24 (0.24;0.24)	1.09 (1.08;1.09)
North Region						
Mortality Rate	174.26 (172.76;175.78)	164.94 (163.48;166.42)	1.06 (1.04;1.07)	249.87 (248.07;251.68)	215.74 (214.07;217.43)	1.16 (1.15;1.17)
Out-of-hospital Mortality Rate	63.55 (62.65;64.47)	47.89 (47.11;48.69)	1.33 (1.30;1.36)	77.84 (76.84;78.86)	57.69 (56.83;58.56)	1.35 (1.32;1.38)
% Deaths at Home	0.36 (0.36;0.37)	0.29 (0.29;0.3)	1.26 (1.25;1.27)	0.31 (0.31;0.32)	0.27 (0.26;0.27)	1.16 (1.16;1.17)
Northeast Region						
Mortality Rate	177.78 (176.92;178.66)	177.12 (176.25;177.99)	1.00 (1.00;1.01)	247.74 (246.72;248.77)	231.32 (230.33;232.31)	1.07 (1.06;1.08)
Out-of-hospital Mortality Rate	70.89 (70.35;71.44)	59.16 (58.66;59.66)	1.20 (1.18;1.21)	86.68 (86.07;87.29)	72.69 (72.14;73.25)	1.19 (1.18;1.20)
% Deaths at Home	0.40 (0.40;0.40)	0.33 (0.33;0.34)	1.19 (1.19;1.20)	0.35 (0.35;0.35)	0.31 (0.31;0.32)	1.11 (1.11;1.12)
Southeast Region						
Mortality Rate	161.86 (161.19;162.52)	163.90 (163.23;164.57)	0.99 (0.98;0.99)	238.88 (238.08;239.69)	219.39 (218.61;220.16)	1.09 (1.08;1.09)
Out-of-hospital Mortality Rate	41.32 (40.98;41.66)	36.05 (35.74;36.37)	1.15 (1.13;1.16)	50.44 (50.07;50.81)	43.52 (43.18;43.87)	1.16 (1.15;1.17)
% Deaths at Home	0.26 (0.25;0.26)	0.22 (0.22;0.22)	1.16 (1.16;1.16)	0.21 (0.21;0.21)	0.20 (0.20;0.20)	1.06 (1.06;1.07)
South Region						
Mortality Rate	155.51 (154.39;156.63)	155.62 (154.51;156.75)	1.00 (0.99;1.01)	238.49 (237.1;239.88)	213.56 (212.25;214.88)	1.12 (1.11;1.13)
Out-of-hospital Mortality Rate	45.70 (45.09;46.31)	40.08 (39.52;40.65)	1.14 (1.12;1.16)	59.51 (58.82;60.21)	50.32 (49.69;50.96)	1.18 (1.16;1.20)
% Deaths at Home	0.29 (0.29;0.30)	0.26 (0.25;0.26)	1.14 (1.13;1.15)	0.25 (0.25;0.25)	0.24 (0.23;0.24)	1.06 (1.05;1.06)
Central West Region						
Mortality Rate	172.9 (171.31;174.50)	163.45 (161.91;165.01)	1.06 (1.04;1.07)	266.52 (264.55;268.51)	228.87 (227.04;230.71)	1.16 (1.15;1.17)
Out-of-hospital Mortality Rate	51.41 (50.55;52.29)	40.67 (39.9;41.45)	1.26 (1.23;1.30)	65.93 (64.95;66.93)	51.85 (50.98;52.73)	1.27 (1.24;1.30)
% Deaths at Home	0.30 (0.29;0.30)	0.25 (0.24;0.25)	1.19 (1.19;1.20)	0.25 (0.24;0.25)	0.23 (0.22;0.23)	1.09 (1.08;1.10)

Table 2: Observed and expected age-standardized mortality rate (for 100,000 inhabitants) and risk ratios for ill-defined causes as underlying causes of death in Brazil and regions, epidemiological weeks 10/2020-39/2021.

Age-standardized Mortality Rate (100k inhabitants) by ill-defined causes, Epidemiological Weeks (10/2020-39/2021), Brazil			
	Observed (CI 95%)	Expected (CI 95%)	Risk Ratio (CI 95%)
Ill-defined causes of death (ICD-10: R00-R09;R96;R98;R99;I46)			
Brazil			
Mortality Rate	44 (43.77;44.22)	30.73 (30.55;30.92)	1.43 (1.42;1.44)
Out-of-hospital Mortality Rate	25.58 (25.41;25.75)	16.9 (16.76;17.04)	1.51 (1.5;1.53)
% Out-of-hospital Deaths	0.58 (0.58;0.58)	0.55 (0.55;0.55)	1.06 (1.05;1.06)
North region			
Mortality Rate	69.2 (68.26;70.16)	48.36 (47.57;49.16)	1.43 (1.4;1.46)
Out-of-hospital Mortality Rate	49.66 (48.87;50.48)	34.16 (33.5;34.83)	1.45 (1.42;1.49)
% Out-of-hospital Deaths	0.72 (0.71;0.73)	0.71 (0.7;0.72)	1.02 (1.01;1.02)
Northeast region			
Mortality Rate	52.17 (51.7;52.64)	36.65 (36.26;37.05)	1.42 (1.4;1.44)
Out-of-hospital Mortality Rate	34.94 (34.56;35.33)	23.79 (23.48;24.11)	1.47 (1.44;1.49)
% Out-of-hospital Deaths	0.67 (0.67;0.67)	0.65 (0.64;0.65)	1.03 (1.03;1.04)
Southeast region			
Mortality Rate	45.72 (45.37;46.07)	32.04 (31.74;32.33)	1.43 (1.41;1.44)
Out-of-hospital Mortality Rate	23.23 (22.97;23.48)	14.88 (14.68;15.08)	1.56 (1.53;1.59)
% Out-of-hospital Deaths	0.51 (0.5;0.51)	0.46 (0.46;0.47)	1.09 (1.09;1.1)
South region			
Mortality Rate	26.57 (26.11;27.03)	19.04 (18.65;19.43)	1.4 (1.36;1.43)
Out-of-hospital Mortality Rate	15.4 (15.05;15.76)	10.41 (10.13;10.71)	1.48 (1.43;1.53)
% Out-of-hospital Deaths	0.58 (0.57;0.59)	0.55 (0.54;0.56)	1.06 (1.05;1.07)
Central-west Region			
Mortality Rate	25.48 (24.87;26.1)	15.04 (14.57;15.51)	1.69 (1.63;1.76)
Out-of-hospital Mortality Rate	13.75 (13.3;14.21)	7.77 (7.44;8.12)	1.77 (1.67;1.87)
% Out-of-hospital Deaths	0.54 (0.53;0.55)	0.52 (0.5;0.53)	1.04 (1.03;1.06)

CI: confidence interval