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Prognostic factors of inhospital death in elderly patients: a time-to-event analysis of a cohort study in Martinique (French West Indies)

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ABSTRACT

Objective The primary objective was to identify predictive factors of inhospital death in a population of patients aged 65 years or older hospitalised with Chikungunya virus (CHIKV) infection. The secondary aim was to develop and validate a predictive score for inhospital death based on the predictors identified.

Design Longitudinal retrospective study from January to December 2014.

Setting University Hospital of Martinique.

Participants Patients aged ≥65 years, admitted to any clinical ward and who underwent reverse transcription PCR testing for CHIKV infection.

Outcome Independent predictors of inhospital death were identified using multivariable Cox regression modelling. A predictive score was created using the adjusted HRs of factors associated with inhospital death. Receiver operating characteristic curve analysis was used to determine the best cut-off value. Bootstrap analysis was used to evaluate internal validity.

Results Overall, 385 patients aged ≥65 years were included (average age: 80±8 years). Half were women, and 35 (9.1%) died during the hospital stay. Seven variables were found to be independently associated with inhospital death (concurrent cardiovascular disorders: HR 11.8, 95% CI 4.5 to 30.8; concurrent respiratory infection: HR 9.6, 95% CI 3.4 to 27.2; concurrent sensorimotor deficit: HR 7.6, 95% CI 2.0 to 28.5; absence of musculoskeletal pain: HR 2.6, 95% CI 1.3 to 5.3; history of alcoholism: HR 2.5, 95% CI 1.1 to 5.9; concurrent digestive symptoms: HR 2.4, 95% CI 1.2 to 4.9; presence of confusion or delirium: HR 2.1, 95% CI 1.1 to 4.2). The score ranged from 0 to 25, with an average of 6±6. The area under the curve was excellent (0.90; 95% CI 0.86 to 0.94). The best cut-off value was a score ≥8 points, with a sensitivity of 91% (82%–100%) and specificity of 75% (70%–80%).

Conclusions Signs observed by the clinician during the initial examination could predict inhospital death. The score will be helpful for early management of elderly subjects presenting within 7 days of symptom onset in the context of CHIKV outbreaks.

INTRODUCTION

Chikungunya virus (CHIKV) infection is an emergent arthropod-borne alpha-virus

Strengths and limitations of this study

► This is the first study to identify independent prognostic factors of inhospital death in a population of elderly subjects infected with Chikungunya virus.
► The sample size is substantial.
► The diagnosis of infection was confirmed in all patients by reverse transcription PCR.
► Our findings warrant external validation.

transmitted by *Aedes* mosquito bites and causes fever with debilitating arthritic illness.[1] [2] CHIKV infection has spread following an endemic–epidemic pattern in Asia, the Indian Ocean Islands and more recently in the French West Indies.[1] Prevalence is high in immunologically naive people,[3–5] and millions of persons have been affected to date.[6] Seroepidemiological surveys in blood donors identified a final seroprevalence of 48.1% in Guadeloupe and 41.9% in Martinique.[7] The mortality and morbidity related to this infection are poorly documented. Some authors have reported excess lethality[8–14] or excess mortality[15 16] during epidemics, or both,[17] with reported rates ranging from 0.1% to 48% according to the study population, location and methods of assessment. Most published findings concern young adults,[8 15 18 19] and although certain authors have suggested that age, comorbidity and alcohol consumption are prognostic factors of death,[11 18 19] mortality and morbidity data are scarce for subjects aged 65 years and over (65+).

Therefore, our primary objective was to identify prognostic factors of inhospital death in a population of patients aged 65+ hospitalised with CHIKV infection. The secondary objective was to develop

a predictive score for inhospital death based on the predictors identified.

METHODS

Study design and subjects

This cohort study was performed in the University Hospital of Martinique (French West Indies) from retrospective cases. Eligible patients were aged 65 years or older, admitted to any clinical ward (including intensive care units (ICUs) and all specialised units) from 10 January to 31 December 2014 and who underwent biological testing using reverse transcription PCR (RT-PCR) for CHIKV infection. Only patients presenting within 7 days of the onset of symptoms were included. There was no concurrent circulation of dengue at the time of the inclusions.

Data collection

Data were retrospectively collected from medical charts. We recorded baseline characteristics, including age and sex, presence or absence of fever and musculoskeletal pain (including arthralgia and myalgia). We also recorded history of diabetes, heart failure or alcoholism and presence or absence of any of the following unusual concurrent clinical manifestations at admission: digestive symptoms (nausea, diarrhoea and abdominal pain), CHIKV-associated central nervous system (CNS) diseases (including confusion or delirium, seizure, syncope, encephalitis and sensorimotor deficit), renal failure, respiratory disorders (including dyspnoea, respiratory infection based on clinical examination, positive sputum Gram stain or culture for bacteria or simply an infiltrate on chest X-ray), cardiovascular disorders (including rhythm disorder, cardiac decompensation and myocardial ischaemia), decompensated diabetes (with negative impact on glycaemic control), dermatological signs (including maculopapular rash, exanthema, erysipelas and purpura) and haematological signs (thrombocytopenia <100X109/L, thrombocytosis >400X109/L, leucocytosis $>0.01x10^9$/L and leucopenia $<0.0015x10^9$/L). The comorbidity burden was assessed using Charlson Comorbidity Index.[20] Charlson Comorbidity Index is a tool that assesses the comorbidity burden for a given individual. It is composed of 19 comorbid conditions including diabetes, with or without complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild or severe liver disease, hemiplegia, renal disease, leukaemia, lymphoma, solid tumour (with or without metastasis) and AIDS. Each of these conditions is weighted by a coefficient (1, 2, 3 or 6) according to their potential influence on mortality. The higher the score, the higher the comorbidity burden. Exanthema, myalgia, back pain, headache, vomiting and diarrhoea without impact on the overall general health status were considered as signs usually accompanying the typical acute phase course of CHIKV infection, in line with the WHO definition.[21] All patients included in this study underwent serum sample testing using RT-PCR with the RealStar Chikungunya RT-PCR Kit (Altona Diagnostics, Hamburg, Germany).

Ethical considerations

The study was performed in accordance with the Declaration of Helsinki and French legislation relating to research involving human beings. According to French law, patients have the right to refuse to participate in studies by notifying their opposition orally.

Statistical analysis

Quantitative variables are described as mean±SD, and categorical variables as number and percentage.

Bivariable relationships between each potential prognostic factor and time to inhospital death were analysed using a Cox model. Variables with a P value of less than 0.2 were entered into the multivariable model. Kaplan-Meier curves were constructed, and the log-rank test was used to test survival differences between score groups (<8 vs ≥8). A multivariable Cox model was constructed to derive the prediction model. Time to inhospital death was the primary outcome. Survival time was defined as the duration between hospital admission and the date of death or date of last contact. The vital status was updated from the hospital wards (using the hospital network data-processing system). Baseline characteristics were considered as potential predictors for inhospital death. A manual stepwise method was used to identify variables independently associated with time to inhospital death, after checking for confounders and interactions. The proportionality of risks over time, which is a condition of validity for the Cox model, was verified graphically.[22] Results are presented as HR and 95% CI.

For the score development, a point value was assigned to each independent factor according to the adjusted HR of the Cox model. Point values were rounded to the nearest integer and summed.

The area under the receiver operating characteristic (AUROC) curve was calculated. Bootstrap analysis was also performed to evaluate the internal validity of the model. Replication on 2000 different samples drawn with replacement was performed using the bootstrap method. The ROC curve was used to determine the cut-off value of the score that best discriminated patients with regard to the outcome. The 95% CI of the AUROC was also obtained using bootstrap methods. The following diagnostic indices and their 95% CI were computed: sensitivity, specificity, positive predictive value and negative predictive value.

A P value <0.05 was considered statistically significant. Statistical analyses were performed using SAS V.9.4 (SAS Institute). The ROC curves were computed using IBM SPSS software release V.21 .

RESULTS

During the epidemic that was ongoing from 10 January to 31 December 2014 in Martinique, 471 patients aged

Table 1 Baseline characteristics of the study population of 385 elderly patients with Chikungunya virus infection
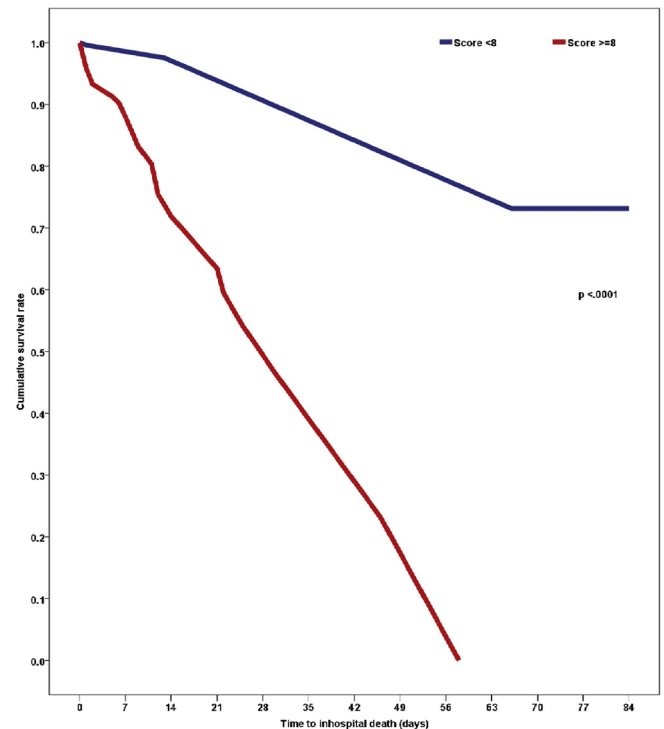
Characteristic	n	%
Age ≥85 years	111	28.8
Female	193	50.1
Fever	331	86.0
Musculoskeletal pain	294	76.4
Including arthralgia	283	73.5
Including myalgia	113	29.4
History of diabetes	145	37.7
History of heart failure	34	8.8
History of alcoholism	36	9.4
Unusual concurrent clinical manifestations		
Digestive symptoms	100	26.0
CNS diseases	180	46.8
Including confusion or delirium	119	30.9
Including sensorimotor deficit	10	2.6
Renal failure	117	30.4
Respiratory disorders	82	21.3
Including respiratory infection	17	4.4
Cardiovascular disorders	97	25.2
Decompensated diabetes	27	7.0
Haematological signs	54	14.0

CNS, central nervous system.

Figure 1 The Kaplan-Meier curves estimate the survival of subjects according to their score groups (score ≥8 vs score <8). The two curves were compared using the log-rank test.

65+ were hospitalised with a diagnosis of CHIKV infection confirmed by RT-PCR. Among these, 86 were not included because the time between onset of symptoms and RT-PCR testing exceeded 7 days. Patients who were excluded did not differ significantly from those who were included in terms of age, sex or comorbidity burden. CHIKV RT-PCR results were available a maximum of 24 hours after blood sampling. In total, 385 patients aged 65 years and over were included in this study. Average age was 80±8 years; half (50.1%) were women. The mean time since symptom onset was 2.4±1.9 days. The average Charlson Comorbidity Index was 1.3±1.4. Other baseline characteristics are presented in table 1.

In all, 35 patients (9.1%) died during the hospital stay. Six patients died in the first 24 hours after admission (16.2%). Thirty-five patients were admitted to the ICU, of whom 16 (45.7%) died during hospital stay. Median time to inhospital death was 58 days (range: 1–84 days). Median length of stay was 7 days (range: 1–84 days). No statistically significant differences were found between deceased and non-deceased patients with regard to age (81.9±9.9 vs 80.3±7.4, respectively) or Charlson Comorbidity Index (1.6±1.3 vs 1.3±1.4, respectively). As shown in figure 1, subjects with score <8 had significantly higher survival rates than those with score ≥8 (P<0.0001).

By multivariable analysis, seven independent predictors of inhospital death were identified, namely concurrent cardiovascular disorders, concurrent respiratory infection, concurrent sensorimotor deficit, absence of musculoskeletal pain, history of alcoholism, concurrent digestive symptoms and presence of confusion or delirium.

The independent predictors of inhospital death are presented in table 2.

Bootstrap methods showed good internal validity of the final model (data not shown).

The point values assigned to each of the predictors identified in the final model are listed in table 2. The scores observed among the study population ranged from 0 to 25; with an average of 6±6. Figure 2 presents the ROC curve. The uncorrected AUROC was as satisfactory as the bootstrapped AUROC, namely 0.90 (95% CI 0.86 to 0.94) and 0.90 (95% CI 0.90 to 0.90), respectively. A score of 8 or higher was considered as the cut-off that best identified patients with a lower risk of inhospital death. The diagnostic performances of the score dichotomised at 8 points are presented in table 3.

DISCUSSION

In our cohort study, seven prognostic factors were associated with in-hospital death (namely cardiovascular disorders, respiratory infection, sensorimotor deficit, absence of musculoskeletal pain, digestive symptoms and presence of confusion or delirium). In all, 9.1% of patients aged 65+ with CHIKV infection died during their hospital stay. This result is similar to those reported by Economopoulou *et al* in 2009[11] in an adult population

Table 2 Independent predictors of inhospital death for elderly patients with CHIKV infection and the corresponding point values of the developed score

| Predictors	HR* (95% CI)	P value	aHR† (95% CI)	P value	Points
Age ≥85 years	1.4 (0.7 to 2.8)	0.36			
Male sex	1.1 (0.6 to 2.2)	0.73			
Fever	1.4 (0.5 to 3.6)	0.51			
Arthralgia‡	0.6 (0.3 to 1.1)	0.10			
Concurrent renal failure‡	3.5 (1.7 to 7.1)	0.0007			
Concurrent decompensated diabetes	0.8 (0.2 to 2.5)	0.66			
Concurrent CNS diseases‡	1.7 (0.8 to 3.3)	0.16			
Including sensorimotor deficit‡	2.8 (0.8 to 9.2)	0.09	7.6 (2.0 to 28.5)	0.003	8
Including confusion or delirium‡	1.9 (0.9 to 3.6)	0.07	2.1 (1.1 to 4.2)	0.04	2
Concurrent cardiovascular disorders‡	6.0 (2.8 to 12.9)	<0.0001	11.8 (4.5 to 30.8)	<0.0001	12
Concurrent respiratory infection‡	3.1 (1.3 to 7.6)	0.01	9.6 (3.4 to 27.2)	<0.0001	10
Absence of musculoskeletal pain‡	2.1 (1.1 to 4.0)	0.04	2.6 (1.3 to 5.3)	0.009	3
History of alcoholism‡	2.5 (1.1 to 5.7)	0.03	2.5 (1.1 to 5.9)	0.04	3
Concurrent digestive symptoms‡	2.2 (1.1 to 4.3)	0.02	2.4 (1.2 to 4.9)	0.02	2

*Unadjusted HR.
†aHR from the final Cox model.
‡Variables proposed to the multivariable model.
aHR, adjusted HR; CHIKV, Chikungunya virus; CNS, central nervous system.

hospitalised during a CHIKV outbreak in Reunion Island with atypical or severe cases (median age: 70 years (range: 15–95 years)). These authors identified alcohol consumption and age over 85 years as prognostic factors of death. In our cohort study, alcohol consumption was also associated with inhospital death, but no significant differences were found between deceased and non-deceased patients with regard to age and comorbidity index. However, in the elderly population, we cannot exclude the possibility that previously undetected comorbidities may flare up in the context of an acute infection.[23] The lack of any difference between those who died and those who survived in terms of comorbidities pleads in favour of a moderate influence of pre-existing disease on the clinical course of CHIKV infection. This is in line with a previous report by Godaert et al[24] about the clinical forms of CHIKV infection in subjects aged 65 years and over during the 2014 outbreak in Martinique. They reported that in almost 70% of cases, elderly patients presented at the acute phase with either an atypical form (ie, fever and arthralgia and one other clinical sign not considered as typical) or a form that is not included in the WHO classification[21] (organ dysfunction, absence of fever and
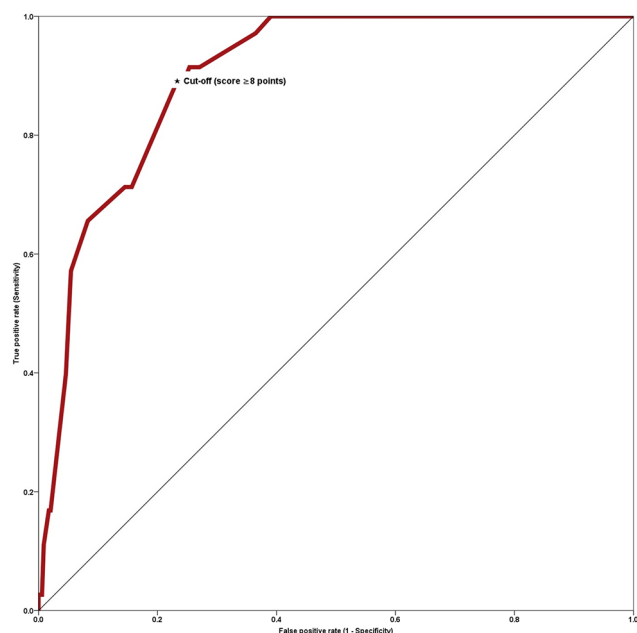
Figure 2 The receiver operating characteristic curve is a plot of the true positive rate (sensitivity) against the false positive rate (1–specificity). The cut-off value represents the point on the curve that maximises both sensitivity and specificity. In this analysis, the cut-off value identified to best distinguish between deceased and non-deceased subjects was 8 points (★).

Table 3 Diagnostic performances of the score dichotomised at 8 points* to predict inhospital death in elderly patients with CHIKV infection.

	Value	95% CI
Sensitivity	91%	82% to 100%
Specificity	75%	70% to 80%
Positive predictive value	26%	18% to 34%
Negative predictive value	99%	98% to 100%
Correctly predicted rate	76%	72% to 80%

*A score ≥8 indicates a higher risk of inhospital death.
CHIKV, Chikungunya virus.

absence of arthralgia, among others). In the report by Godaert et al,[24] patients aged 65 years or over who had the typical form of CHIKV had fewer comorbidities than aged patients in whom the CHIKV presentation was severe or unclassifiable. In the younger group, only patients with an unclassifiable form had more comorbidities. At a similar level of comorbidities, elderly subjects did not have severe forms more frequently than their younger counterparts. Therefore, it would seem that pre-existing disease cannot alone explain the excess of mortality in the elderly population.

In this cohort study, symptoms present at admission appear to be predictive of the clinical course. WHO recently established definitions for acute, atypical and severe cases of CHIKV infection.[21] Dysfunction of at least one organ system that is life-threatening and requires hospitalisation defines severe clinical cases of CHIKV infection. In the literature, seroprevalence of CHIKV infection and the risk of hospitalisation increase with age,[7 25] and older people are reportedly at greater risk of presenting atypical or severe clinical cases of CHIKV infection.[11 17 24] In our cohort study, cardiovascular disorders, respiratory infection, sensorimotor deficit, absence of musculoskeletal pain, digestive symptoms and presence of confusion or delirium were identified as independent predictors of inhospital death. These signs were also observed in patients without known underlying conditions and, therefore, seem to be integral components of the clinical presentation at the acute phase in this population. These signs can be observed by the clinician during the initial examination and appear to be very informative. In patients with a positive diagnosis of CHIKV, the presence of these signs could guide therapeutic management.

Considering all the predictive factors identified by multivariable analysis, we developed a score to predict the risk of inhospital death in older patients with CHIKV infection. It was derived using usual and accurate statistical methods. Moreover, its internal validation was very good. Indeed, the accuracy of our score was excellent (AUROC=0.90) and remained unchanged between iterations of internal validation using the bootstrap method. During an outbreak, this score could be very helpful since the signs or symptoms that are components of the score are not among the clinical features usually described in CHIKV infection.[21] The score is easy to calculate by simply summing the different point values corresponding to the seven predictors. A cut-off of less than 8 points identifies patients who are at lower risk of dying during their hospital stay, with excellent discriminant properties.

Patients with CHIKV infection with clinical signs suggestive of likely adverse outcome should receive specialised care from a medical team including a specialist in geriatric medicine. Ellis et al[26] suggested in their meta-analysis that geriatric intervention increases a patient's likelihood of being alive after an emergency admission to hospital. This practice is becoming increasingly common in some medical specialities, such as oncology.

Some limitations of this study deserve to be underlined, and the findings must be interpreted with caution. Our study concerned only hospitalised patients, presenting within 7 days of the onset of symptoms. We do not have data regarding patients admitted more than 7 days after onset of symptoms. All data were collected from medical files. The absence of a documented symptom does not necessarily mean that the patient did not experience this symptom. For instance, the number of CHIKV-associated CNS disease would have been underestimated, leading thus to information bias. All patients had atypical or severe clinical cases of CHIKV infection according to definitions of the expert group of WHO.[21] Although Godaert et al recently showed that around 70% of elderly patients present with these clinical forms, we do not have information about mortality in patients presenting with typical acute clinical cases of CHIKV infection. Patients may have received different interventions after admission (ie, ICU admission vs general ward), which may also have affected mortality. The main limitation regarding the score relates to the absence of external validation. However, as outbreaks are rare, as are geriatric care units involved in CHIKV research, it is very challenging to constitute a validation cohort.

A strong point of this study is the fact that it is, to the best of our knowledge, the first study to identify predictors of in-hospital death in a population of elderly subjects infected by CHIKV. Among the other strengths of our study, we can underline the fact that all subjects included underwent RT-PCR serum testing in the same laboratory, using the same commercial kit. Furthermore, the sample size is large.

In conclusion, our results show that CHIKV infection can be fatal in atypical or severe clinical cases. A score based on easy-to-access clinical features obtained in routine practice could identify patients at higher risk of adverse outcomes during the hospital stay. This score could be helpful to guide management and patient supervision in the context of CHIKV outbreaks.

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