Health care index score and risk of death following TB diagnosis in HIV-infected patients

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Introduction

Tuberculosis (TB) in HIV-positive persons remains a great challenge for physicians globally. Survival rates of HIV-infected persons with active TB (HIV/TB patients) vary substantially around the world and depends on several factors relating to the management of both HIV infection and TB disease. Among such factors, the most important are: prompt and proper diagnosis of TB, including culture and resistance tests; timely initiation of adequate TB treatment, as well as assessment of a patient's immune status and timely initiation of combination antiretroviral therapy (cART). (1;2) These factors are mainly related to and depend on the local level of health care and availability of resources. Incidence rates of TB among HIV- infected persons would naturally be higher in regions with a high prevalence of *Mycobacterium tuberculosis* (MTB) infection in the general population, while mortality rates are likely to be higher in settings with a high prevalence of multi-drug resistant (MDR) TB. (3-7) However, even in resource-limited settings with a high prevalence of TB it is possible to achieve a significant reduction in TB associated mortality among HIV/TB patients. (8;9)

We have previously reported a number of patient characteristics relating to both HIV (i.e. having AIDS or poor immune status) and TB (i.e. having disseminated or rifamycin-resistant disease) were associated with an increased risk of death. In addition, some aspects reflective of patient care such as not including a rifamycin in first line TB therapy or not commencing cART were independent predictors of death. (6) These factors, however, could only partially explain regional differences in mortality, suggesting that other patient or health care associated factors may have differed between the geographic regions.

The purpose of the current analysis was to evaluate the extent of appropriate health care provided to HIV/TB patients across different geographical regions by establishing a Health Care Index (HCI), and to use this HCI to generate an HIV/TB HCI score that reflects health care utilisation. We then analysed the cumulative probability of death in patients stratified by HCI score

and regional differences in hazards of death in multivariable models incorporating the HCI score.

Methods

Patient cohort

The HIV/TB study is an international cohort of consecutive HIV-infected patients diagnosed with TB who initiated anti-TB treatment between January 2004 and December 2006 at one of the 52 participating clinics in Europe and Argentina. The present analysis is based on 1061 HIV/TB patients whose HIV infection was diagnosed prior to or up to one month after TB diagnosis to avoid bias when assessing HIV management. Details of the study have been published elsewhere. (6) Briefly, information was collected retrospectively on a standardised case report forms (CRF) and included demographic and clinical characteristics of the TB disease, details of smear, culture and resistance tests performed, drug regimens used and TB outcomes. Information on the underlying HIV infection was collected on a separate CRF and included all available CD4-cell count and HIV-RNA measurements, use of antiretroviral drugs, presence of AIDS defining illnesses (other than TB) and use of chemoprophylaxis. (10)

Health care index

To evaluate aspects of TB and HIV health care, we chose a number of health care parameters that reflected the actual care provided to patients rather than disease specific characteristics (e.g. 'having a culture or resistance test performed' rather than 'disease caused by drug resistant *Mycobacterium tuberculosis'*). These parameters were combined in a health care index, for which the following components were a priori considered:

1. World Health Organization (WHO) defined definite diagnosis of TB: culture confirmed disease due to MTB and/or at least one sputum smear examination positive for acid-fast bacilli (AFB). (11)

2. The undertaking of an MTB drug resistance test.

3. Inclusion of rifamycin (R), isoniazid (H) and pyrazinamide (Z) in the initial TB treatment regimen.

4. Availability of at least one CD4-cell count measurement between 6 months prior to and 1 month after TB diagnosis.

5. Initiation of cART (combination of at least 3 antiretroviral drugs from any class) prior to or up to one month after TB diagnosis.

The one month cut off for CD4-cell counts and use of cART was chosen to reduce survival bias as substantial early mortality was observed. In sensitivity analyses, we assessed the effects of initiation of cART within 3, 6, 3-9 and >9 months of TB diagnosis, and CD4-cell count measurements obtained within 2, 3 and 6 months of TB diagnosis

Statistical analysis

The study population was divided into four geographical regions according to the country of residence: EE (N=573), CNE (N=166), SE (N=208) and AR (N=114)[1]. Descriptive statistics were used to compare patient characteristics and the HCI components across regions. The HCI components were considered as quantitative discrete variables (Yes/No), and given a score of zero if no information was available for a given patient. The proportion of patients to whom each HCI component applied was calculated and compared by region. Follow-up was from the date of TB diagnosis till last clinic visit (or date of loss to follow-up), date of death or one year after TB diagnosis, whichever occurred first. TB was classified as pulmonary, if disease was limited to lungs and/or pleura; extrapulmonary, if TB was limited to any other single organ system; or disseminated, if it was miliary TB, TB in at least two organ systems, or if MTB had been isolated from blood or bone marrow.

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[1] Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): Denmark, France, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR)

To establish an HCI score, the relative hazard of death for each HCI component was calculated using a multivariable Cox model incorporating all 5 HCI components. A weighted score was then assigned to each significant HCI component based on the natural logarithm of its relative hazard of death. The mean HCI score was calculated for each region and compared to the proportion of patients who died within 12 months of TB diagnosis and to those with successful TB outcomes (cure/treatment completion).

Kaplan-Meier survival analysis was used to estimate the probability of death within 12 months of TB diagnosis among patients stratified by HCI score. Cox proportional hazard models were used to analyse the effect of the HCI score on mortality. Other factors included in the Cox model were those that were previously shown to be associated with mortality and included: gender, CD4-cell count at TB diagnosis, prior AIDS diagnosis, previous TB diagnosis, TB rifamycin resistance, and site of TB. (6)

Results

Patient population

A total of 1061 HIV/TB patients were included in the analysis. Patient characteristics are presented in Table 1. As reported previously, patients from EE were younger and more often had a history of injection drug use (IDU) and/or hepatitis C co-infection. (6) Approximately half of all patients had disseminated TB, and the majority of patients had established HIV infection at the time of TB diagnosis. Patients from AR had more profound immunodeficiency, while patients from EE had less advanced HIV infection.

The proportion of patients with positive values for each HCI component differed significantly by geographic region (Table 1). Fewer patients in EE had a definite TB diagnosis, initiated RHZ-containing TB therapy or received cART. Patients in EE and AR less often had TB drug resistance tests and CD4-cell counts performed.

Health care index score

To develop an HCI score, the five selected components were included in a Cox model with death as the dependent variable (Table 2). Use of cART, RHZ-containing initial TB treatment and having a resistance test performed were associated with a reduced hazard of death in both univariable and multivariable models. The availability of a CD4-cell count and a definite TB diagnosis were not associated with a reduced hazard of death in either univariable or multivariable analysis (Table 2). Consequently, these components were not included in the final HCI score. Similar results were obtained when using different time windows for CD4-cell count measurements or cART initiation (data not shown). Of note, having culture-based definite TB diagnosis (i.e. excluding patients with only positive smear tests) was highly correlated (R=82%, p<0.0001) with having resistance test performed. Including smear positive tests in the definite

diagnosis decreased this correlation to 62% and reduced the association between definite

diagnosis and risk of death to an insignificant level.

The natural logarithms of the three relative hazards (RH) of death were used to weigh the

components that make up the HCI score. As the effects of initial treatment with RHZ and use of

cART were approximately double the magnitude of the effect of resistance testing, resistance

testing was assigned 1 point and the use of RHZ-containing initial TB treatment and use of cART 2

points each. The HCI score could thus range from 0 to 5 with a higher score indicative of more

intensive health care utilisation (Table 2).

An HCI score was calculated for each patient. The distribution of HCI scores for each

region is displayed in Figure 1. The majority (54-82%) of patients from CNE, SE and AR had HCI

scores $\geq$3 compared with only 29% of patients from EE (p<0.0001), where 28% in EE had an HCI

score of 0. The mean HCI score was highest in CNE (3.2 [95% CI 3.1-3.3]), followed by SE (3.0 [2.9-

3.2]) and AR (2.9 [2.6-3.0]), and was lowest in EE (1.6 [1.5-1.7]), p<0.0001.

Health care index score and TB treatment outcome

Treatment outcome was available for 995 (98%) patients. Overall, successful TB outcome

was reported for 578 patients (58%) and commonest in regions with the highest HCI scores.

Similarly, Kaplan-Meier estimates of being alive at 12 months were highest in regions with the

highest HCI scores (Figure 2). A progressive reduction in 12 month cumulative mortality from 39%

(95% CI: 31% - 48%) for patients with HCI = 0, to 9% (6% - 13%) for those with HCI ≥ 4 was

observed (p<0.0001) (Figure 3). When the HCI score was incorporated in unadjusted Cox models of

death within 12 months of TB diagnosis, a 38% reduction in mortality (RH 0.62 (95% CI 0.56 –

0.70), p<0.0001) for each unit increase in HCI score was observed (Table 3). This association

remained significant (RH 0.73 (0.64-0.84)) after adjustment for other factors that could potentially

affect prognosis of HIV/TB patients (gender, CD4-cell count at TB diagnosis, prior TB or AIDS

diagnosis, rifamycin resistance, and site of TB) (Table 3). However, despite the significant predictive value of the HCI score, patients from EE remained at approximately 3-fold increased risk of death compared with the other regions after adjustment for HCI score.

Sensitivity analyses

A number of sensitivity analyses were performed (Table 3) to test the performance of the score in various subpopulations. Overall, the results of these analyses were consistent with the main finding that the HCI score was a significant predictor of one-year mortality in HIV/TB patients. For example, when restricting analysis to IDU patients (N=521) or patients from Eastern Europe (N= 573), a one unit increase in HCI score was associated with 24% and 27% reductions in mortality, respectively. In analysis restricted to patients with pan-susceptible TB (N=337), a one unit increase in HCI score was associated with a 27% reduction in mortality, although this was insignificant in the multivariable model likely due to the small sample size. Furthermore, when restricting endpoints to only TB- and AIDS-related deaths (excluding deaths from any other causes), a one unit increase in HCI score reduced mortality by 15%. Finally, when the HCI score was included in the model as a categorical variable, one year mortality was 45% lower in patients with an HCI score of 1 and 72% lower in those with HCI scores of 4/5 compared with patients with an HCI score of 0 (Table 3).

Discussion

In this study we assessed and compared health care utilization for HIV/TB patients by using a number of health care parameters. These parameters were further used to generate a HCI score as a measure of health care utilization. HCI score was predictive of mortality in HIV/TB patients. A one unit HCI score increase was independently associated with a 27% reduced risk of death within the first year after TB diagnosis. However, the observed regional differences in mortality among HIV/TB patients in Europe and Argentina were only partly explained by differences in health care utilization. While the use of RHZ-based anti-TB therapy, TB drug susceptibility testing and early use of cART are to be implemented as a priority, further research is required to explain the profound regional differences in HIV and TB outcomes and propose additional measures to harmonize these outcomes.

The HCI score presented here can be implemented and used for two main purposes: evaluation and comparison of health care utilisation for HIV/TB patients and predicting patients' prognosis. It can be implemented and assessed by health care authorities at various levels, from a single clinic to programme, country and region. Further, it can contribute to establishment of a benchmark of health care utilization for HIV/TB patients by identification a best performing facility. The advantage of this HCI score is that it includes a set of simple and widely used diagnostic and treatment procedures, which should be available in both high- and low-income settings. Our HCI score is based on the health care parameters that previously have been found to be independently associated with the outcome of HIV/TB patients (5;6;12). The predictive value of the HCI score remained highly significant when the model was adjusted for other factors that might play a role in patients' outcome (Table 3), suggesting that this association is not a result of a confounding.

Optimal management of TB includes early case detection and initiation of effective anti-TB therapy. Increased frequency of sputum-smear negativity in HIV-patients requires performance of culture test, which has been shown to be more sensitive in HIV/TB patients (13;14). Culture and drug resistance testing are essential in TB diagnosis to ensure effective therapy is administered, especially in settings with a high prevalence of MDR-TB. (15;16) Conventional culture and resistance testing are disadvantaged by advanced laboratory set-up and long incubation time. Early detection of resistant MTB strains is critical particularly in high prevalent MDR-TB settings in order to adjust treatment regimen and prevent transmission of drug-resistant strains. Thus, there is a critical need for diagnosis of TB to be more rapid and reliable and less costly, than is currently the case in many resource limited settings. (17-19) Rapid tests for simultaneous molecular detection of MTB and drug-resistant strains should be widely implemented and used. (17)

As approximately 50% of our patients had disseminated TB, relying solely on sputum samples may not be sufficient to make a definite TB diagnosis and culture or molecular diagnostics of lymph node aspirates, blood or bone marrow may need to be more widely undertaken to obtain MTB isolates for drug susceptibility testing and thus fulfilling this HCI component. (20;21)

Successful outcome of TB treatment relies on a treatment regimen of high quality drugs to which the MTB isolate is susceptible, given at the correct dose and for a sufficient duration. (1;21) WHO recommends that empiric anti-TB treatment should, as a minimum, include a rifamycin, isoniazid, and pyrazinamide (RHZ-based), with the addition of 2-3 second-line anti-TB drugs if resistance is suspected. (22) When results of drug-susceptibility testing become available, the regimen should be individualised accordingly. In our study, the use of RHZ-based regimens as initial TB therapy and outcome were strongly correlated, even after adjustment for region of residence. (6) While this may reflect clinicians' decisions to avoid RHZ in patients with poor outcome such as those with significant liver injury (i.e. HCV coinfected) (23), universal

implementation of RHZ-based regimens to treat HIV/TB in EE is an inexpensive measure to improve patient outcomes. More importantly, if second line anti-TB drugs are added while the results of resistance tests are awaited, amplification of TB drug resistance in partially resistant MTB isolates may be avoided and transmission of drug-resistant TB reduced. Further research is needed to investigate underlying reasons for not initiating RHZ-based therapy in EE.

Two recent studies have addressed the timing of cART in HIV/TB patients (24-26). Both studies provided evidence for early cART initiation in patients with CD4-cell counts <50 cells/mm3. In addition, the SAPIT study showed benefit from cART use during TB therapy rather than deferral of cART until TB treatment is completed, even in patients with CD4-cell counts >200 cells/mm3. We observed that few patients were receiving cART prior to TB diagnosis or up to one month after TB diagnosis, irrespective of region of residence, and many of our patients did not commence cART during TB treatment. Our HCI model suggests benefit from early cART use in HIV/TB patients, which is consistent with the results of the above clinical trials and provides support for the notion that all HIV/TB patients should start cART while still receiving TB therapy. For most patients, cART may be safely deferred until the end of the intensive TB treatment phase, although patients with low CD4-cell counts or other evidence of immunosuppression, and possibly those infected with MDR TB, should start cART at the earliest opportunity (within 2 weeks of starting anti-TB treatment) (25;26). In EE especially, this will require improved access to cART for marginal groups of the population (i.e. IDUs, prisoners, alcohol addicts, etc) and adherence support to those who start cART (27). Finally, when making decision to initiate cART in HIV/TB patients the benefits and risks should be carefully weighed for each individual patient considering potential toxicities and drug-drug interactions, probability of IRIS, adherence issues, etc.

There are some limitations to this study. Due to the retrospective design, some data could be missed or not available for collection. In order to ensure the completeness of data

collection, an extensive quality assurance programme has been performed, which included queries to the sites and monitoring visits. We were able to define the HCI score using variables, measured within the study; however there are may be other variables, which we were not able to capture. Although we included health care parameters known to be associated with patients' outcome (5;6;12), other factors including, e.g. prevalence of primary MDR-TB, use of second-line anti-TB drugs, presence of integrated HIV and TB services, may affect outcomes. Future studies are needed, designed around these factors to enable identification of measures that may further improve HIV/TB outcomes, particularly in EE. Experience from South Africa has shown that integration of HIV and TB services helps to improve patients' management and thus survival. (28) Health care infrastructure differs in Eastern Europe and is characterised by separate management of HIV and TB in different hospitals by different specialists, where the collaboration and data exchange may not be well developed. A sensitivity analysis including only patients from Eastern Europe, showed results consistent with the main analysis: a higher HCI score was associated with improved survival. The HCI score also did not change when models were stratified by an individual centre or country (data not shown). The HCI score needs to be validated in independent cohorts of HIV/TB patients in Europe and elsewhere. This is planned in a prospective extension of the HIV/TB study, which has now been initiated (www.cphiv.dk).

HIV/TB programmes in developing world are encouraged to implement service integration, drug susceptibility testing and early cART initiation in HIV/TB patients. (29) The HCI score presented here may serve as a tool to predict the benefits of such interventions. Further refinement of the health care parameters, for instance by adding additional components, e.g. HIV/TB-service integration, duration of TB treatment, treatment changes according to the TB drug-resistance patterns, use of directly observed therapy, use of co-trimoxazole prophylaxis, and adherence may enhance its clinical usefulness.

Conclusions

We developed a HCI score which reflects health care utilisation in HIV/TB patients and which predicts outcome. The HCI is easy to apply in both high- and low-income settings, and if validated in other populations, may assist the planning of programmatic interventions. Our results suggest that the outcome of HIV/TB patients may be improved by implementing several measures, including MTB drug susceptibility testing, use of RHZ-based anti-TB therapy and early use of cART.

Table 1. Baseline characteristics and health care index components in HIV/TB patients stratified by geographical region

	Eastern Europe N = 573	Southern Europe N = 208	Central Northern Europe N = 166	Argentina N = 114	P
Patient characteristics N, %					
Male gender	410 (71.6)	160 (76.9)	78 (47.0)	73 (64.0)	<0.0001
IDU (as risk factor for TB) [a]	409 (71.9)	63 (34.6)	19 (13.0)	30 (26.6)	<0.0001
Hepatitis C AB positive [b]	268 (46.9)	53 (25.5)	15 (9.0)	15 (13.2)	<0.0001
Disseminated TB [c]	349 (60.9)	104 (50.0)	86 (51.8)	57 (50.0)	<0.0001
Rifamycin resistant TB [d]	121 (45.8)	5 (3.5)	5 (4.5)	6 (16.2)	<0.0001
Prior AIDS [e]	79 (13.8)	42 (20.2)	22 (13.3)	63 (55.3)	<0.0001
Median (IQR)					
Age, years	30.2 (26.2 – 35.0)	37.7 (31.8 – 43.5)	37.4 (31.6 – 44.2)	35.5 (30.2 – 41.7)	<0.0001
CD4-cell count, cells/μl [f]	210 (85 – 463)	132.5 (46 – 291)	140 (50.5 – 293.5)	92 (40 – 233.5)	<0.0001
HIV-RNA, log10 copies/ml [g]	5.1 (4.3 – 5.7)	4.9 (3.5 – 5.6)	4.9 (3.4 – 5.6)	4.6 (3.5 – 5.4)	0.023
Health Care Index components (N, %)					
Definite TB diagnosis	389 (67.9)	167 (80.3)	136 (81.9)	82 (71.9)	0.0002
Resistance test performed [h]	264 (84.9)	141 (87.6)	111 (85.4)	37 (69.8)	<0.0001
RHZ-containing initial TB treatment	258 (45.0)	163 (78.4)	146 (88.0)	96 (84.2)	<0.0001
CD4-cell count measurement performed from 6 months prior to 1 month after TB diagnosis	316 (55.2)	161 (77.4)	126 (75.9)	67 (58.8)	<0.0001
cART started prior to or within 1 month of TB diagnosis	98 (17.1)	112 (53.9)	87 (52.4)	54 (47.4)	<0.0001

Footnote Table 1

Eastern Europe (EE): Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe (CNE): France, Denmark, Switzerland, United Kingdom; Southern Europe (SE): Italy, Spain; Argentina (AR)

Baseline defined as the date of TB diagnosis

(a) TB risk factor was unknown for 51 patients: EE 4 (7.8%), SE 26 (51.0%), CNE 20 (39.2%), AR 1 (2.0%), p<0.0001

(b) Hepatitis C antibody (AB) status was unknown for 528 patients No significant differences comparing the proportions with unknown

HCV AB status across the regions, p=0.13

(c) Disseminated TB - TB involving more than one organ-system, miliary TB, or *Mycobaterium tuberculosis* isolated from blood or bone marrow
(d) Proportion of those with resistance test performed
(e) AIDS defined using the 1993 Centers for Disease Control and Prevention clinical case definitions (category C).
(f) CD4-cell count was unknown for 208 patients: EE 146 (25.5%), SE: 14 (6.7%), CNE 22 (13.3%), AR 26 (22.8%), p<0.0001
(g) HIV-RNA was unknown for 547 patients: EE 467 (81.5%), SE 23 (11.1%), CNE 11 (6.6%), AR 46 (40.4%), p<0.0001
(h) Proportion of those with positive culture for *Mycobaterium tuberculosis* (N with culture confirmed TB 311, 161, 130, 53 in EE, SE, CNE and AR respectively)

Table 2. Cox proportional hazard model used to calculate the weighted Health Care Index (HCI) score

HCI component	Univariable			Multivariable			Final			Ln RH*	HCI Score weighting
	RH	95% CI	p	RH	95% CI	p	RH	95% CI	p		
Definite diagnosis	0.76	0.54 – 1.05	0.097	1.18	0.79 – 1.78	0.42					**0**
Resistance test performed	0.63	0.47 – 0.86	0.0031	0.65	0.45 – 0.95	0.025	0.71	0.53 – 0.97	0.031	-0.34	**1**
Initial TB treatment with RHZ	0.37	0.28 – 0.51	<0.0001	0.41	0.30 – 0.57	<0.0001	0.43	0.31 – 0.58	<0.0001	-0.85	**2**
CD4 measured from 6 months prior to or up to 1 month after TB diagnosis	0.90	0.66 – 1.23	0.50	1.22	0.89 – 1.68	0.21					**0**
cART started prior to or up to 1 month after TB diagnosis	0.32	0.21 – 0.48	<0.0001	0.35	0.23 – 0.53	<0.0001	0.36	0.24 – 0.55	<0.0001	-1.02	**2**

*Ln (natural logarithm) RH (relative hazard) is calculated from the RHs of death obtained in the final model
Absence of a HCI component yielded a zero score. The HCI score was calculated for each patient as the sum of each of the HCI components.

Figure 1. Distribution of patients according to health care index (HCI) score and region of residence
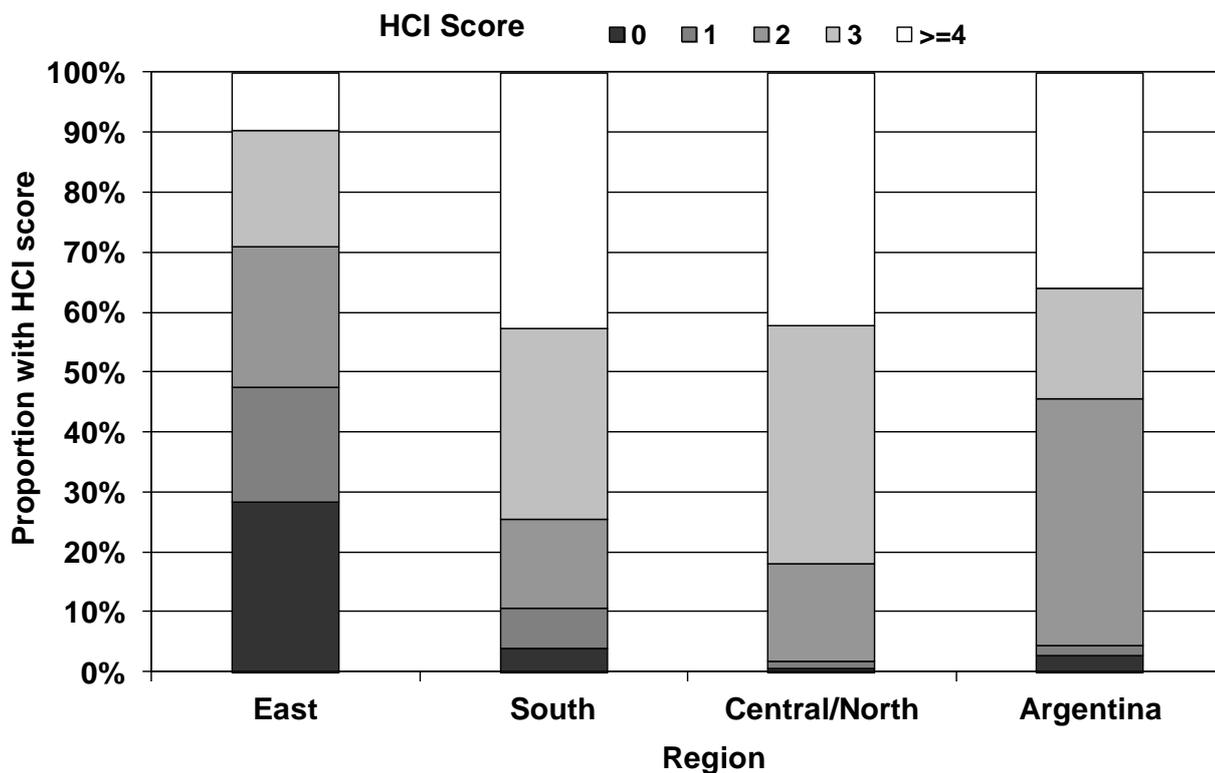
N with HCI score:

HCI Score	East	South	Central/North	Argentina
0	140	4	1	3
1	132	18	2	2
2	112	23	20	37
3	134	74	73	31
≥4	55	89	70	41

EE, Eastern Europe; SE, Southern Europe; CNE, Central/Northern Europe; AR, Argentina

Figure 2. Mean Health Care Index score and outcomes in HIV/TB patients stratified by region of residence
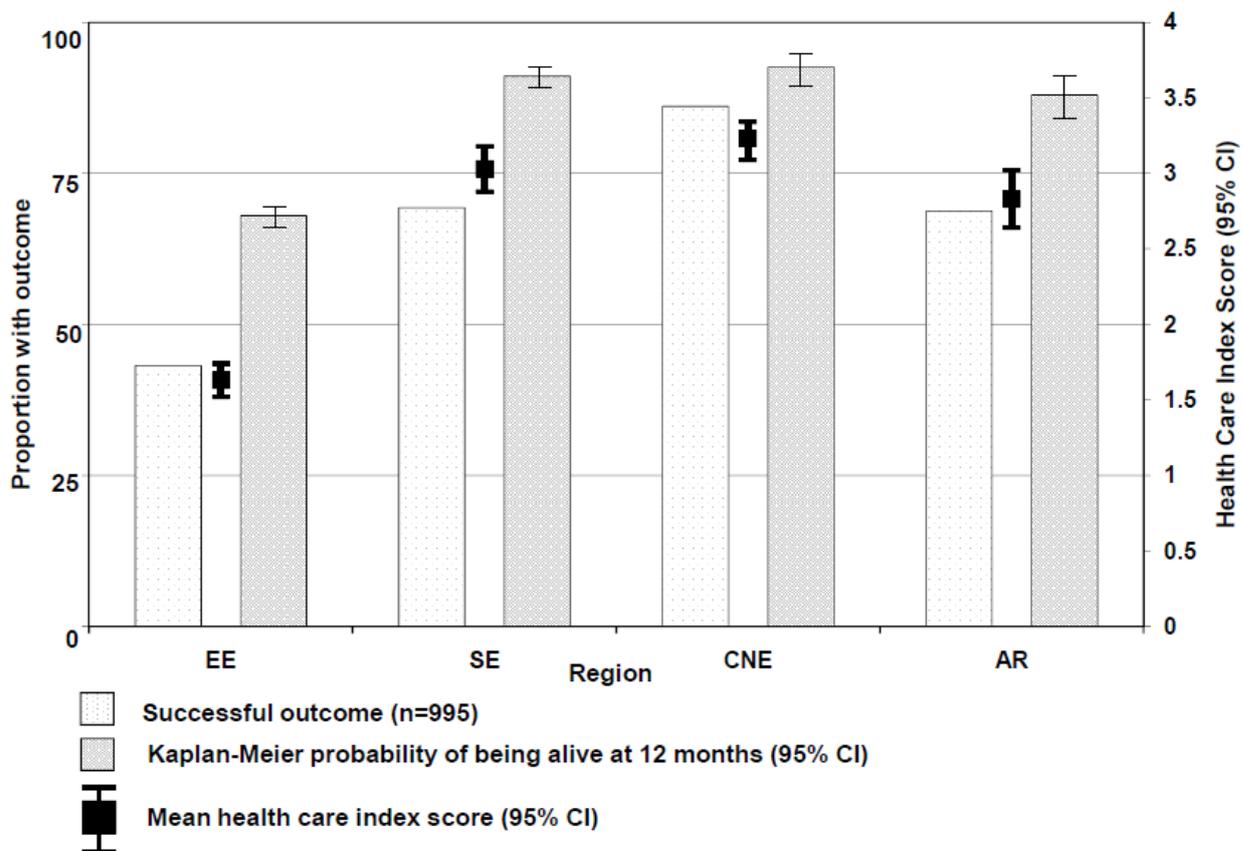
Mean HCI score (95% CI): Eastern Europe (EE) 1.63 (1.52 – 1.74); Southern Europe (SE) 3.03 (2.88 - 3.18); Central/Northern Europe (CNE) 3.22 (3.09 – 3.34); Argentina (AR) 2.83 (2.64 – 3.02)

Figure 3. Kaplan-Meier probability of death in patients stratified according to their HCI score

N under follow-up

HCI score:

HCI score			
0	148	67	45
1	154	105	78
2	192	132	103
3	312	256	220
≥4	255	233	211
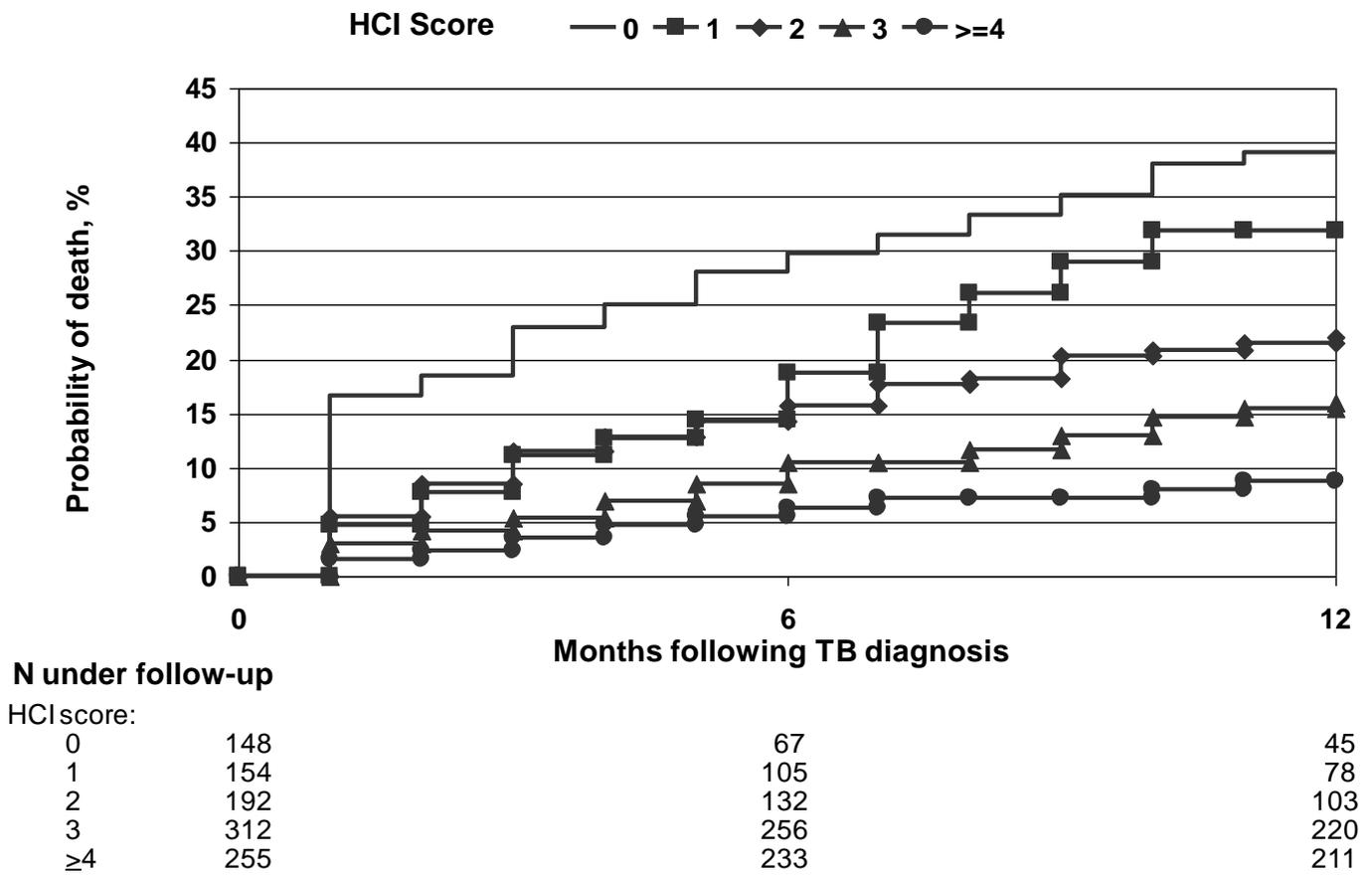
Table 3. Univariable and multivariable relative hazard (RH) of death within 12 months of TB diagnosis

	Univariable		Multivariable			
			Not including HCI score		Including HCI score	
	RH (95% CI)	p	RH (95% CI)	P	RH (95% CI)	p
Health care index score (per 1 unit increase)	0.62 (0.56 – 0.70)	<0.0001			0.73 (0.64 – 0.84)	<0.0001
Region — Eastern Europe	1.00		1.00		1.00	
Region — Southern Europe	0.14 (0.07 – 0.28)	<0.0001	0.13 (0.06 – 0.25)	<0.0001	0.19 (0.09 – 0.39)	<0.0001
Region — Central/Northern Europe	0.16 (0.08 – 0.32)	<0.0001	0.17 (0.08 – 0.35)	<0.0001	0.27 (0.13 – 0.58)	0.0007
Region — Argentina	0.28 (0.14 – 0.54)	0.0002	0.22 (0.11 – 0.45)	<0.0001	0.31 (0.25 – 0.64)	0.0015
Sensitivity analyses						
HCI Score (per 1 unit increase) in:						
- Patient with pan-susceptible TB, N=337	0.70 (0.50-0.97)	<0.032			0.73 (0.50-1.07)	0.10
- Injecting Drug users, N=521	0.69 (0.60-0.80)	<0.0001			0.76 (0.66-0.87)	0.0004
- Patients from Eastern Europe, N=573	0.76 (0.67-0.87)	<0.0001			0.73 (0.64-0.84)	<0.0001
Only including TB- and AIDS-related deaths	0.83 (0.73-0.94)	0.0044			0.85 (0.73-0.99)	0.042
Score — 0	1.00				1.00	
Score — 1	0.70 (0.45-1.10)	0.12			0.55 (0.35-0.86)	0.0082
Score — 2	0.50 (0.33-0.76)	0.0010			0.57 (0.38-0.85)	0.0064
Score — 3	0.33 (0.21-0.50)	<0.0001			0.40 (0.25-0.63)	0.0001
Score — ≥ 4	0.09 (0.05-0.19)	<0.0001			0.28 (0.16-0.49)	<0.0001

Multivariable model adjusted also for gender, CD4-cell count at TB diagnosis (below or above 200 cells/mm^3), prior AIDS, previous diagnosis of TB, presence of *Mycobacteria* strains resistant to at least rifampicin, location of TB (pulmonary, extrapulmonary, disseminated

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The role of each co-author:

Daria Podlekareva contributed in project development and coordination, data analysis and interpretation, and was responsible for writing the manuscript

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