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Data Article

Data on prognostic factors associated with 3-month and 1-year mortality from infective endocarditis

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ABSTRACT

This article describes supplementary tables and figures associated with the research paper entitled "Impact of referral bias on prognostic studies outcomes: insights from a population-based cohort study on infective endocarditis". The aforementioned paper is a secondary analysis of data from the *EI 2008* cohort on infective endocarditis and aimed at characterising referral bias. A total of 497 patients diagnosed with definite infective endocarditis between January 1st and December 31st 2008 were included in *EI 2008*. Data were collected from hospital medical records by trained clinical research assistants. Patients were divided into three groups: admitted to a tertiary hospital (group T), admitted to a non-tertiary hospital and referred secondarily to a tertiary hospital (group NTT) or admitted to a non-tertiary hospital and

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not referred (group NT). The pooled (NTT+T) group mimicked studies recruiting patients in tertiary hospitals only. Two different starting points were considered for follow up: date of first hospital admission and date of first admission to a tertiary hospital if any (hereinafter referred to as "referral time"). Referral bias is a type of selection bias which can occur due to recruitment of patients in tertiary hospitals only (excluding those who are admitted to non-tertiary hospitals and not referred to tertiary hospitals). This bias may impact the description of patients' characteristics, survival estimates as well as prognostic factors identification. The six tables presented in this paper illustrate how patients' selection (population-based sample [pooled (NT+NTT+T) group] versus recruitment in tertiary hospitals only [pooled (NTT+T) group]) might impact Hazards Ratios values for prognostic factors. Crude and adjusted Cox regression analyses were first performed to identify prognostic factors associated with 3-month and 1-year mortality in the whole sample using inclusion as the starting point. Analyses were then performed in the pooled (NTT+T) group first using inclusion as the starting point and finally using referral time as the starting point. Figures 1 to 3 illustrate how HR increase with time for covariates that were considered as time-varying covariates (covariate*time interaction).

Specifications Table

Subject	Medicine
Specific subject area	Epidemiology; Infectious Diseases
Type of data	Tables and figures
How data were acquired	Secondary analysis of data from the *EI 2008* cohort on infective endocarditis
Data format	Analysed
Parameters for data collection	Patients presenting with a diagnosis of definite infective endocarditis (Duke criteria modified by Li) and admitted to a hospital between January 1st 2008 and December 31st 2008 in one of the seven participating French regions were included in the *EI 2008* cohort. All the patients included in *EI 2008* were considered for our analyses.
Description of data collection	Baseline and follow-up data were collected from hospital medical records by trained clinical research assistants and a standardized case report form was completed. Vital status was collected from hospitals medical records, general practitioners' records or civil registry one year after inclusion in the *EI 2008* cohort.
Data source location	Institution: CHRU Nancy City/Town/Region: Nancy Country: France Latitude and longitude for collected samples/data: 46.2276° N, 2.2137° E
Data accessibility	The datasets generated during and/or analysed during the current study are not publicly available due to restrictions pertaining to the French law, but are available from the corresponding author upon reasonable request.
Related research article	Collonnaz M, Erpelding M-L, Alla F, Goehringer F, Delahaye F, Iung B, et al. Impact of referral bias on prognostic studies outcomes: insights from a population-based cohort study on infective endocarditis. Annals of Epidemiology [Internet]. 2020 Sep; Available from: https://doi.org/10.1016/j.annepidem.2020.09.008 [1]

Value of the Data

- Studies recruiting patients in tertiary hospitals only are subject to referral bias. The results presented in the tables are part of a comprehensive analysis of the impact of this bias. They illustrate how referral bias can impact the assessment of the prognostic value of factors associated with 3-month and 1-year mortality from infective endocarditis.
- Practitioners involved in infective endocarditis management as well as public health researchers and epidemiologists may benefit from these data. In addition, any researcher considering an observational study of a rare disease prone to be managed in non-tertiary hospitals at some point may benefit from these data.
- These data may be useful for researchers aiming at characterising the impact of referral bias in studies on infective endocarditis or on other rare diseases. They can also be useful for future research on infective endocarditis as we highlighted the importance on a population-based recruitment of patients.

1. Data Description

The tables are supplementary data associated with the research paper entitled "Impact of referral bias on prognostic studies outcomes: insights from a population-based cohort study on infective endocarditis" [1]. The aforementioned paper is a secondary analysis of data from the *EI 2008* cohort and aimed at characterising referral bias.

Tables 1 to 3 refer to the identification of prognostic factors associated with 3-month mortality from infective endocarditis (IE). Tables 4 to 6 refer to the identification of prognostic factors associated with to 1-year mortality.

Tables 1 and 4 present absolute frequency, crude and adjusted Hazards Ratios (HR) when using the whole sample of patients (pooled (NT+NTT+T) group) and using the date of inclusion (date of first admission to hospital for IE) as the starting point for analyses.

Tables 2 and 5 present absolute frequency, crude and adjusted HRs obtained when performing analyses on a sample of patients recruited in tertiary hospitals only (pooled (NTT+T) group) using date of inclusion as the starting point.

Tables 3 and 6 present absolute frequency, crude and adjusted HRs obtained when recruiting patients in tertiary hospitals only (pooled (NTT+T) group) using referral time (the date of first admission to a tertiary hospital if any) as the starting point.

A total of six prognostic factors were associated with 3-month mortality (age $\geq$70, Charlson comorbidity index $\geq$2, Staphylococcal IE, septic shock, cerebral embolism, and serum creatinine level $\geq$18 μmol/L). The prognostic factors did not differ across groups; however, the values of HRs associated with these prognostic factors were influenced by sample and starting point selection.

When using the date of inclusion as the starting point, a total of nine prognostic factors were associated with 1-year mortality in the whole sample and in the pooled (NTT+T) group (age $\geq$70, Charlson comorbidity index $\geq$2*time, high blood pressure*time, heart failure*time, Staphylococcal IE, valve perforation, septic shock, cerebral embolism, and serum creatinine level $\geq$180 μmol/L). When using referral time as the starting point, heart failure and valve perforation were no longer identified as prognostic factors.

Figs. 1 to 3 represent the evolution of Hazard Ratios with time (in days) for the three covariates (Charlson comorbidity index $\geq$2, high blood pressure and heart failure) that did not meet the proportional hazard assumption and were included in 1-year survival models as time-varying covariates (considering covariate*time interaction). Figs. 1 to 3 show how HR for these covariates increased with time. For example, for Charlson comorbidity index $\geq$2, the risk of death from IE in the whole sample was multiplied by 1.27 [1.09–1.47] after one month and by 1.61 [1.20–2.17] after two months. Noteworthy, 95% confidence intervals width also increased with time, showing a loss of precision in HR estimates over time.

Table 1
Factors associated with 3-month mortality in the whole sample (pooled (NT+NTT+T) group) (Starting point=inclusion)

	Whole sample (N=460)						
		Crude association			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p
Socio-demographic							
Age				**<0.001**			**<0.001**
< 70	280	ref	-		ref	-	
≥70	180	2.212	1.495-3.274		2.350	1.535-3.597	
Sex				0.226			
Female	117	ref	-				
Male	343	0.771	0.505-1.175				
Medical history							
Charlson Comorbidity index				**<0.001**			**0.009**
<2	248	ref	-		ref	-	
≥ 2	212	2.196	1.466-3.288		1.760	1.150-2.695	
High blood pressure				**0.006**			
No	242	ref	-				
Yes	218	1.741	1.172-2.587				
Injection drug use				0.242			
No	435	ref	-				
Yes	25	0.504	0.160-1.588				
Underlying heart disease (HD)				0.491			
No previously known HD	236	ref	-				
Previously known HD without prosthetic valve	125	0.818	0.505-1.326				
Prosthetic valve	99	1.148	0.714-1.847				
Previous IE				0.119			
No	430	ref	-				
Yes	30	0.401	0.127-1.264				
Cardiac implantable electronic device				0.464			
No	399	ref	-				
Yes	61	1.221	0.716-2.082				

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Table 1 (*continued*)

	Whole sample (N=460)						
		Crude association			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p
IE profile							
Clinical characteristics							
Suspected source of infection				**0.071**			
Community	344	ref	-				
Healthcare-related, acquired in hospital	103	1.510	0.982-2.323				
Healthcare-related, not acquired in hospital	13	2.096	0.845-5.201				
Left heart endocarditis				0.390			
No	90	ref	-				
Yes	370	1.257	0.747-2.115				
Fever				0.586			
No	65	ref	-				
Yes	395	1.175	0.657-2.103				
Heart failure				**0.043**			
No	303	ref	-				
Yes	157	1.499	1.013-2.218				
Microbiological characteristics							
Staphylococcal IE				**<0.001**			**0.010**
No	293	ref	-		ref	-	
Yes	167	2.500	1.691-3.697		1.695	1.132-2.539	
Echocardiographic characteristics							
Vegetation				0.625			
No vegetation	59	ref	-				
≤15mm	204	0.856	0.459-1.597				
>15mm	117	1.176	0.613-2.254				
Unknown size of vegetation	80	0.997	0.488-2.034				
Perforation				0.445			
No	375	ref	-				
Yes	85	0.812	0.476-1.385				

(*continued on next page*)

Table 1 (*continued*)

	Whole sample (N=460)						
		Crude association			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p
IE complications							
*Cardiac abscess***				**0.048**			
No	361	ref	-				
Yes	99	1.677	1.005-2.799				
*Septic shock***				**<0.001**			**<0.001**
No	385	ref	-		ref	-	
Yes	75	5.463	3.647-8.183		3.873	2.480-6.049	
*Cerebral haemorrhage***				**0.002**			
No	427	ref	-				
Yes	33	2.584	1.414-4.724				
*Cerebral embolism***				**<0.001**			**<0.001**
No	363	ref	-		ref	-	
Yes	97	2.619	1.721-3.988		2.490	1.556-3.884	
Vascular phenomena				0.083			
No	242	ref	-				
Yes	218	1.412	0.956-2.085				
Immunologic phenomena				0.893			
No	405	ref	-				
Yes	55	0.960	0.525-1.752				
Persistent sepsis despite treatment				0.085			
No	410	ref	-				
Yes	50	1.599	0.938-2.727				
Serum creatinine level ≥180 µmol/L				**<0.001**			**<0.001**
No	327	ref	-		ref	-	
Yes	133	4.857	3.254-7.248		3.160	2.081-4.797	

Crude and adjusted Cox regressions were performed.

* Stepwise selection, sle=0.20, sls=0.05

** Time dependent covariate6 patients from group NTT were excluded from this analysis because they were not referred yet at 3 months.

Table 2
Factors associated with 3-month mortality in patients who were managed in a tertiary hospital (Pooled (NTT+T) group) (Starting point=inclusion)

	Pooled (NTT+T) group (N=404)								
		Crude association			Adjusted association[+]			Adjusted association[*]	
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Socio-demographic										
Age				**0.001**			**<0.001**			**<0.001**
< 70	256	ref	-		ref	-		ref	-	
≥ 70	148	2.085	1.361-3.193		2.368	1.494-3.755		2.368	1.494-3.755	
Sex				0.391						
Female	99	ref	-							
Male	305	0.813	0.507-1.304							
Medical history										
Charlson Comorbidity index				**0.002**			**0.020**			**0.020**
<2	226	ref	-		ref	-		ref	-	
≥ 2	178	2.011	1.303-3.105		1.712	1.087-2.699		1.712	1.087-2.699	
High blood pressure				**0.005**						
No	222	ref	-							
Yes	182	1.851	1.202-2.852							
Injection drug use				0.362						
No	381	ref	-							
Yes	23	0.585	0.185-1.851							
Underlying heart disease (HD)				0.379						
No previously known HD	208	ref	-							
Previously known HD without prosthetic valve	106	0.747	0.433-1.291							
Prosthetic valve	90	1.157	0.695-1.926							
Previous IE				0.182						
No	376	ref	-							
Yes	28	0.457	0.144-1.445							
Cardiac implantable electronic device				0.531						
No	347	ref	-							
Yes	57	1.201	0.677-2.130							

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Table 2 (*continued*)

	Pooled (NTT+T) group (N=404)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE profile										
Clinical characteristics										
Suspected source of infection				0.100						
Community	300	ref	-							
Healthcare-related, acquired in hospital	93	1.541	0.967-2.457							
Healthcare-related, not acquired in hospital	11	2.061	0.747-5.687							
Left heart endocarditis				0.384						
No	79	ref	-							
Yes	325	1.290	0.727-2.288							
Fever				0.361						
No	54	ref	-							
Yes	350	1.380	0.692-2.754							
Heart failure				0.088						
No	262	ref	-							
Yes	142	1.452	0.946-2.229							
Microbiological characteristics										
Staphylococcal IE				**<0.001**			**0.006**			**0.006**
No	259	ref	-		ref	-		ref	-	
Yes	145	2.733	1.777-4.204		1.863	1.191-2.914		1.863	1.191-2.914	
Echocardiographic characteristics										
Vegetation				0.495						
No vegetation	52	ref	-							
≤15mm	173	0.965	0.476-1.958							
>15mm	104	1.414	0.685-2.922							
Unknown size of vegetation	75	1.045	0.470-2.326							
Perforation				0.396						
No	324	ref	-							
Yes	80	0.780	0.440-1.384							

(*continued on next page*)

Table 2 (*continued*)

	Pooled (NTT+T) group (N=404)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE complications										
Cardiac abscess[**]				**0.022**						
No	309	ref	-							
Yes	95	1.869	1.094-3.193							
Septic shock [**]				**<0.001**			**<0.001**			**<0.001**
No	340	ref	-		ref	-		ref	-	
Yes	64	5.288	3.387-8.254		3.622	2.209-5.937		3.622	2.209-5.937	
Cerebral haemorrhage[**]				**0.001**						
No	375	ref	-							
Yes	29	2.941	1.559-5.548							
Cerebral embolism[**]				**<0.001**			**<0.001**			**<0.001**
No	315	ref	-		ref	-		ref	-	
Yes	89	2.618	1.662-4.125		2.563	1.567-4.190		2.563	1.567-4.190	
Vascular phenomena				0.193						
No	210	ref	-							
Yes	194	1.328	0.866-2.034							
Immunologic phenomena				0.711						
No	353	ref	-							
Yes	51	1.123	0.610-2.067							
Persistent sepsis despite treatment				0.219						
No	358	ref	-							
Yes	46	1.449	0.803-2.615							
Serum creatinine level ≥180 µmol/L				**<0.001**			**<0.001**			**<0.001**
No	285	ref	-		ref	-		ref	-	
Yes	119	4.533	2.928-7.019		3.048	1.935-4.799		3.048	1.935-4.799	

Crude and adjusted Cox regressions were performed.

[*] Stepwise selection, sle=0.20, sls=0.05

[+] Covariates resulting from the selection process in the whole sample were forced into the model

[**] Time dependent covariate6 patients from group NTT were excluded from this analysis because they were not referred yet at 3 months.

Table 3
Factors associated with 3-month mortality in patients who were managed in a tertiary hospital (Pooled (NTT+T) group) (Starting point=referral time)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association*			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Socio-demographic										
Age				**0.001**			**<0.001**			**<0.001**
< 70	261	ref	-		ref	-		ref	-	
≥ 70	149	2.108	1.376-3.228		2.316	1.463-3.666		2.316	1.463-3.666	
Sex										
Female	100	ref	-	0.335						
Male	310	0.793	0.494-1.271							
Medical history										
Charlson Comorbidity index				**0.001**			**0.029**			**0.029**
<2	230	ref	-		ref	-		ref	-	
≥ 2	180	2.038	1.320-3.145		1.662	1.054-2.621		1.662	1.054-2.621	
High blood pressure				**0.005**						
No	225	ref	-							
Yes	185	1.857	1.206-2.861							
Injection drug use				0.359						
No	386	ref	-							
Yes	24	0.583	0.184-1.845							
Underlying heart disease (HD)				0.399						
No previously known HD	212	ref	-							
Previously known HD without prosthetic valve	107	0.762	0.441-1.316							
Prosthetic valve	91	1.168	0.701-1.945							
Previous IE				0.196						
No	382	ref	-							
Yes	28	0.467	0.148-1.479							
Cardiac implantable electronic device				0.599						
No	3511	ref	-							
Yes	59	1.166	0.658-2.069							

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Table 3 (*continued*)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE profile										
Clinical characteristics										
Suspected source of infection				0.090						
Community	304	ref	-							
Healthcare-related, acquired in hospital	95	1.559	0.978-2.486							
Healthcare-related, not acquired in hospital	11	2.082	0.754-5.746							
Left heart endocarditis				0.354						
No	82	ref	-							
Yes	328	1.311	0.739-2.336							
Fever				0.374						
No	55	ref	-							
Yes	355	1.368	0.686-2.730							
Heart failure				0.085						
No	266	ref	-							
Yes	144	1.458	0.950-2.239							
Microbiological characteristics										
Staphylococcal IE				**<0.001**			**0.007**			**0.007**
No	263	ref	-		ref	-		ref	-	
Yes	147	2.732	1.776-4.202		1.854	1.186-2.899		1.854	1.186-2.899	
Echocardiographic characteristics										
Vegetation				0.544						
No vegetation	52	ref	-							
≤15mm	176	0.968	0.477-1.963							
>15mm	106	1.387	0.671-2.866							
Unknown size of vegetation	76	1.036	0.465-2.306							
Perforation				0.443						
No	330	ref	-							
Yes	80	0.799	0.451-1.418							

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Table 3 (*continued*)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE complications										
Cardiac abscess[**]				0.060						
No	315	ref	-							
Yes	95	1. 669	0.979-2.846							
Septic shock[**]				**<0.001**			**<0.001**			**<0.001**
No	345	ref	.		ref	-		ref	-	
Yes	65	5.057	3.239-7.894		3.462	2.119-5.657		3.462	2.119-5.657	
Cerebral haemorrhage[**]				**0.001**						
No	381	ref	-							
Yes	29	2.830	1.500-5.336							
Cerebral embolism[**]				**<0.001**			**<0.001**			**<0.001**
No	321	ref	-		ref	-		ref	-	
Yes	89	2.579	1.638-4.061		2.518	1.544-4.105		2.518	1.544-4.105	
Vascular phenomena				0.181						
No	214	ref	-							
Yes	196	1.338	0.874-2.051							
Immunologic phenomena				0.674						
No	359	ref	-							
Yes	51	1.140	0.619-2.099							
Persistent sepsis despite treatment				0.160						
No	364	ref	.							
Yes	46	1.528	0.846-2.758							
Serum creatinine level ≥180 µmol/L				**<0.001**			**<0.001**			**<0.001**
No	291	ref	-		ref	-		ref	-	
Yes	119	4.683	3.024-7.251		3.133	1.990-4.932		3.133	1.990-4.932	

Crude and adjusted Cox regressions were performed.

[*] Stepwise selection, sle=0.20, sls=0.05

[+] Covariates resulting from the selection process in the whole sample were forced into the model

[**] Time dependent covariate

Table 4
Factors associated with 1-year mortality in the whole sample (pooled (NT+NTT+T) group) (Starting point=inclusion)

		Whole sample (N=466)					
		Crude association			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p
Socio-demographic							
Age				**<0.001**			**<0.001**
< 70	285	ref	-		ref	-	
≥70	181	2.495	1.764-3.529		2.402	1.653-3.489	
Sex				0.103			
Female	118	ref	-				
Male	348	0.736	0.509-1.064				
Medical history							
*Charlson Comorbidity index***				**<0.001**			**0.001**
<2	252	ref	-		ref	-	
≥ 2	214	1.011	1.006-1.016		1.008	1.003-1.013	
*High blood pressure***				**<0.001**			**0.006**
No	245	ref	-		ref	-	
Yes	221	1.008	1.004-1.012		1.006	1.002-1.010	
Injection drug use				0.079			
No	440	ref	-				
Yes	26	0.358	0.114-1.125				
Underlying heart disease (HD)				0.806			
No previously known HD	240	ref	-				
Previously known HD without prosthetic valve	126	0.887	0.588-1.338				
Prosthetic valve	100	1.029	0.667-1.587				
Previous IE				0.078			
No	436	ref	-				
Yes	30	0.408	0.151-1.105				
Cardiac implantable electronic device				0.276			
No	403	ref	-				
Yes	63	1.289	0.816-2.038				

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Table 4 (*continued*)

		Whole sample (N=466)					
		Crude association			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p
IE profile							
Clinical characteristics							
Suspected source of infection				**0.033**			
Community	348	ref	-				
Healthcare-related, acquired in hospital	105	1.540	1.055-2.246				
Healthcare-related, not acquired in hospital	13	2.010	0.879-4.599				
Left heart endocarditis				0.471			
No	93	ref	-				
Yes	373	1.177	0.756-1.831				
Fever				0.559			
No	66	ref	-				
Yes	400	1.164	0.699-1.937				
*Heart failure***				**0.001**			**0.027**
No	307	ref	-		ref	-	
Yes	159	1.006	1.002-1.009		1.004	1.000-1.007	
Microbiological characteristics							
Staphylococcal IE				**<0.001**			**0.004**
No	297	ref	-		ref	-	
Yes	169	2.179	1.548-3.067		1.679	1.177-2.395	
Echocardiographic characteristics							
Vegetation				0.885			
No vegetation	59	ref	-				
≤15mm	207	1.051	0.596-1.855				
>15mm	119	1.221	0.669-2.231				
Unknown size of vegetation	81	1.099	0.573-2.106				
Perforation				0.143			**0.020**
No	381	ref	-		ref	-	
Yes	85	0.690	0.420-1.134		0.545	0.327-0.909	

(*continued on next page*)

Table 4 (*continued*)

		Whole sample (N=466)					
		Crude association			Adjusted association*		
	n	HR	95% CI	p	HR	95% CI	p
IE complications							
*Cardiac abscess***				0.283			
No	367	ref	-				
Yes	99	1.299	0.806-2.096				
*Septic shock***				**<0.001**			**<0.001**
No	390	ref	-		ref	-	
Yes	76	4.129	2.840-6.003		3.360	2.211-5.104	
*Cerebral haemorrhage***				**0.015**			
No	433	ref	-				
Yes	33	2.042	1.151-3.622				
*Cerebral embolism***				**<0.001**			**<0.001**
No	369	ref	-		ref	-	
Yes	97	2.256	1.545-3.293		2.324	1.556-3.469	
*Vascular phenomena****				0.182			
No	246	ref	-				
Yes	220	0.998	0.094-1.001				
Immunologic phenomena				0.272			
No	411	ref	-				
Yes	55	0.717	0.396-1.298				
Persistent sepsis despite treatment				0.091			
No	416	ref	-				
Yes	50	1.521	0.936-2.474				
Serum creatinine level ≥180 µmol/L				**<0.001**			**<0.001**
No	333	ref	-		ref	-	
Yes	133	3.996	2.832-5.638		2.780	1.944-3.977	

Crude and adjusted Cox regressions were performed.

* Stepwise selection, sle=0.20, sls=0.05

** Time dependent covariate

*** Time-varying covariate (interaction with time)

Table 5
Factors associated with 1-year mortality in patients who were managed in a tertiary hospital (Pooled (NTT+T) group) (Starting point=inclusion)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Socio-demographic										
Age				**<0.001**			**<0.001**			**<0.001**
< 70	261	ref	-		ref	-		ref	-	
≥ 70	149	2.253	1.543-3.290		2.193	1.460-3.293		2.193	1.460-3.293	
Sex				0.271						
Female	100	ref	-							
Male	310	0.791	0.521-1.200							
Medical history										
Charlson Comorbidity index[***]							**0.005**			**0.005**
<2	230	ref	-	**<0.001**	ref	-		ref	-	
≥ 2	180	1.009	1.005-1.014		1.007	1.002-1.012		1.007	1.002-1.012	
High blood pressure[***]							**0.007**			**0.007**
No	225	ref	-	**<0.001**	ref	-		ref	-	
Yes	185	1.008	1.004-1.013		1.006	1.002-1.011		1.006	1.002-1.011	
Injection drug use				0.144						
No	386	ref	-							
Yes	24	0.425	0.135-1.340							
Underlying heart disease (HD)				0.664						
No previously known HD	212	ref	-							
Previously known HD without prosthetic valve	107	0.862	0.541-1.373							
Prosthetic valve	91	1.106	0.694-1.760							
Previous IE				0.149						
No	382	ref	-							
Yes	28	0.479	0.177-1.302							
Cardiac implantable electronic device				0.341						
No	351	ref	-							
Yes	59	1.272	0.775-2.088							

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Table 5 (*continued*)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE profile										
Clinical characteristics										
Suspected source of infection				0.075						
Community	304	ref	-							
Healthcare-related, acquired in hospital	95	1.484	0.978-2.253							
Healthcare-related, not acquired in hospital	11	2.071	0.836-5.129							
Left heart endocarditis				0.268						
No	82	ref	-							
Yes	328	1.331	0.802-2.208							
Fever				0.362						
No	55	ref	-							
Yes	355	1.322	0.725-2.408							
Heart failure[***]				**<0.001**			**0.017**			**0.017**
No	266	ref	-		ref	-		ref	-	
Yes	144	1.007	1.003-1.011		1.005	1.001-1.009		1.005	1.001-1.009	
Microbiological characteristics										
Staphylococcal IE				**<0.001**			**0.015**			**0.015**
No	263	ref	-		ref	-		ref	-	
Yes	147	2.153	1.476-3.141		1.634	1.102-2.423		1.634	1.102-2.423	
Echocardiographic characteristics										
Vegetation				0.607						
No vegetation	52	ref	-							
≤15mm	176	1.221	0.633-2.358							
>15mm	106	1.523	0.768-3.022							
Unknown size of vegetation	76	1.191	0.567-2.503							
Perforation				0.178			**0.047**			**0.047**
No	330	ref	-		ref	-		ref	-	
Yes	80	0.694	0.408-1.181		0.574	0.332-0.992		0.574	0.332-0.992	

(*continued on next page*)

Table 5 (*continued*)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE complications										
Cardiac abscess[**]				0.116						
No	315	ref	-							
Yes	95	1.491	0.906-2.455							
Septic shock [**]				**<0.001**			**<0.001**			**<0.001**
No	345	ref	-		ref	-		ref	-	
Yes	65	3.962	2.610-6.013		2.991	1.874-4.773		2.991	1.874-4.773	
Cerebral haemorrhage[**]				**0.005**						
No	381	ref	-							
Yes	29	2.386	1.308-4.352							
Cerebral embolism[**]				**<0.001**			**<0.001**			**<0.001**
No	321	ref	-		ref	-		ref	-	
Yes	89	2.184	1.443-3.307		2.266	1.452-3.535		2.266	1.452-3.535	
Vascular phenomena[***]				0.105						
No	214	ref	-							
Yes	196	0.997	0.993-1.001							
Immunologic phenomena				0.624						
No	359	ref	-							
Yes	51	0.861	0.472-1.568							
Persistent sepsis despite treatment				0.166						
No	364	ref	-							
Yes	46	1.455	0.856-2.475							
Serum creatinine level ≥180 µmol/L				**<0.001**			**<0.001**			**<0.001**
No	291	ref	-		ref	-		ref	-	
Yes	119	3.942	2.693-5.770		2.882	1.941-4.278		2.882	1.941-4.278	

Crude and adjusted Cox regressions were performed.

[*] Stepwise selection, sle=0.20, sls=0.05

[+] Covariates resulting from the selection process in the whole sample were forced into the model

[**] Time dependent covariate

[***] Time-varying covariate (interaction with time)

Table 6
Factors associated with 1-year mortality in patients who were managed in a tertiary hospital (Pooled (NTT+T) group) (Starting point=referral time)

	Pooled (NTT+T) group (N=410)								
		Crude association			Adjusted association+			Adjusted association*	
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Socio-demographic										
Age				**<0.001**			**<0.001**			**<0.001**
< 70	261	ref	-		ref	-		ref	-	
≥ 70	149	2.343	1.586-3.462		2.310	1.520-3.511		2.317	1.526-3.518	
Sex				0.261						
Female	100	ref	-							
Male	310	0.781	0.508-1.201							
Medical history										
*Charlson Comorbidity index****				**0.003**			**0.036**			**0.022**
<2	230	ref	-		ref	-		ref	-	
≥ 2	180	1.008	1.003-1.013		1.005	1.000-1.010		1.006	1.001-1.011	
*High blood pressure****				**0.001**			**0.005**			**0.004**
No	225	ref	-		ref	-		ref	-	
Yes	185	1.011	1.005-1.018		1.009	1.003-1.016		1.009	1.003-1.016	
Injection drug use				0.201						
No	386	ref	-							
Yes	24	0.473	0.150-1.491							
Underlying heart disease (HD)				0.453						
No previously known HD	212	ref	-							
Previously known HD without prosthetic valve	107	0.823	0.505-1.343							
Prosthetic valve	91	1.180	0.738-1.887							
Previous IE				0.193						
No	382	ref	-							
Yes	28	0.515	0.190-1.400							
Cardiac implantable electronic device				0.507						
No	351	ref	-							
Yes	59	1.193	0.709-2.008							

(*continued on next page*)

Table 6 (*continued*)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE profile										
Clinical characteristics										
Suspected source of infection				**0.039**						
Community	304	ref	-							
Healthcare-related, acquired in hospital	95	1.581	1.031-2.422							
Healthcare-related, not acquired in hospital	11	2.239	0.902-5.558							
Left heart endocarditis				0.324						
No	82	ref	-							
Yes	328	1.300	0.772-2.188							
Fever				0.520						
No	55	ref	-							
Yes	355	1.219	0.667-2.226							
Heart failure[***]				**0.006**			0.081			
No	266	ref	-		ref	-				
Yes	144	1.006	1.002-1.011		1.004	1.000-1.008				
Microbiological characteristics										
Staphylococcal IE				**<0.001**			**0.020**			**0.017**
No	263	ref	-		ref	-		ref	-	
Yes	147	2.225	1.508-3.283		1.618	1.079-2.426		1.633	1.092-2.443	
Echocardiographic characteristics										
Vegetation				0.729						
No vegetation	52	ref	-							
≤15mm	176	1.153	0.594-2.235							
>15mm	106	1.413	0.708-2.820							
Unknown size of vegetation	76	1.131	0.534-2.394							
Perforation				0.118			**0.038**			
No	330	ref	-		ref	-				
Yes	80	0.638	0.363-1.121		0.543	0.305-0.966				

(*continued on next page*)

Table 6 (*continued*)

	Pooled (NTT+T) group (N=410)									
		Crude association			Adjusted association[+]			Adjusted association[*]		
	n	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
IE complications										
Cardiac abscess[**]				0.132						
No	315	ref	-							
Yes	95	1.469	0.891-2.422							
Septic shock [**]				**<0.001**			**<0.001**			**<0.001**
No	345	ref	-		ref	-		ref	-	
Yes	65	4.086	2.679-6.233		2.847	1.754-4.621		2.766	1.721-4.445	
Cerebral haemorrhage[**]				**0.003**						
No	381	ref	-							
Yes	29	2.494	1.364-4.558							
Cerebral embolism[**]				**<0.001**			**<0.001**			**<0.001**
No	321	ref	-		ref	-		ref	-	
Yes	89	2.336	1.536-3.555		2.499	1.581-3.949		2.551	1.615-4.029	
Vascular phenomena[***]				0.168						
No	214	ref	-							
Yes	196	0.997	0.993-1.001							
Immunologic phenomena				0.810						
No	359	ref	-							
Yes	51	0.929	0.509-1.697							
Persistent sepsis despite treatment				0.171						
No	364	ref	-							
Yes	46	1.466	0.848-2.536							
Serum creatinine level ≥180 µmol/L				**<0.001**			**<0.001**			**<0.001**
No	291	ref	-		ref	-		ref	-	
Yes	119	4.113	2.776-6.095		3.085	2.053-4.634		3.055	2.031-4.594	

Crude and adjusted Cox regressions were performed.

[*] Stepwise selection, sle=0.20, sls=0.05

[+] Covariates resulting from the selection process in the whole sample were forced into the model

[**] Time dependent covariate

[***] Time-varying covariate (interaction with time)

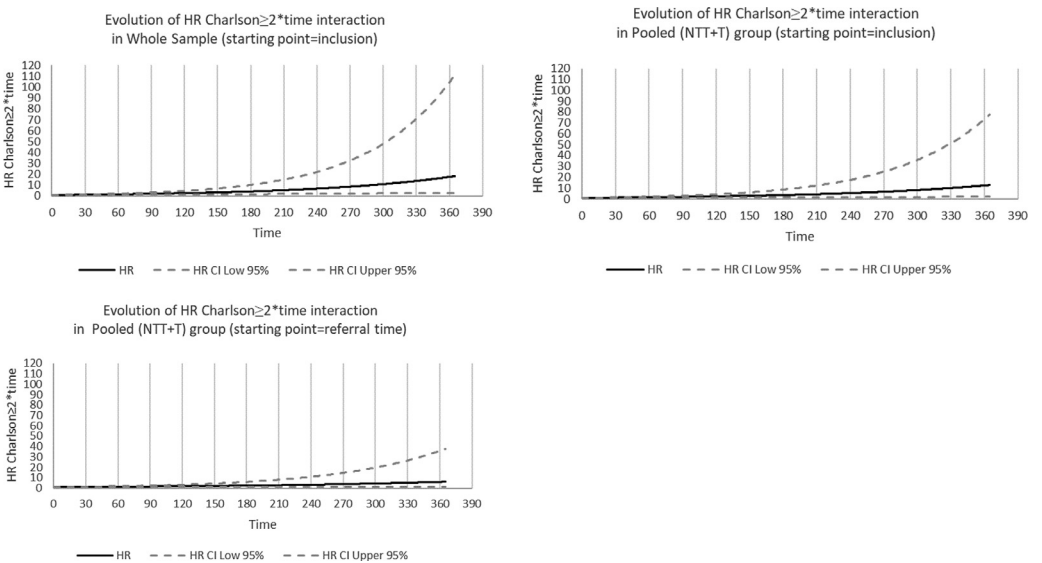

Fig. 1. Evolution over time of Hazard Ratios for the association between Charlson comorbidity index ≥2 and one-year mortality.

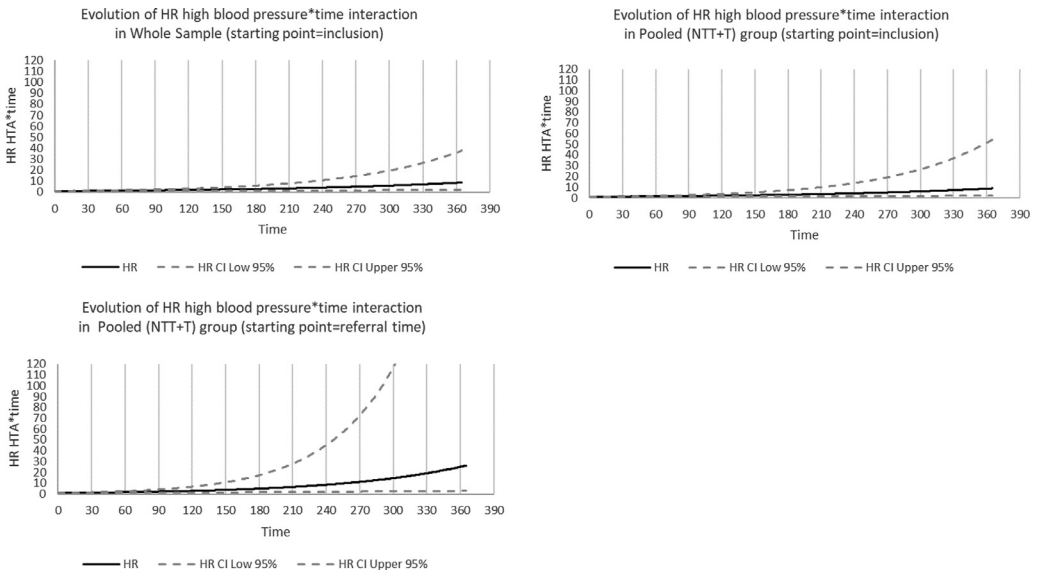

Fig. 2. Evolution over time of Hazard Ratios for the association between high blood pressure and one-year mortality.

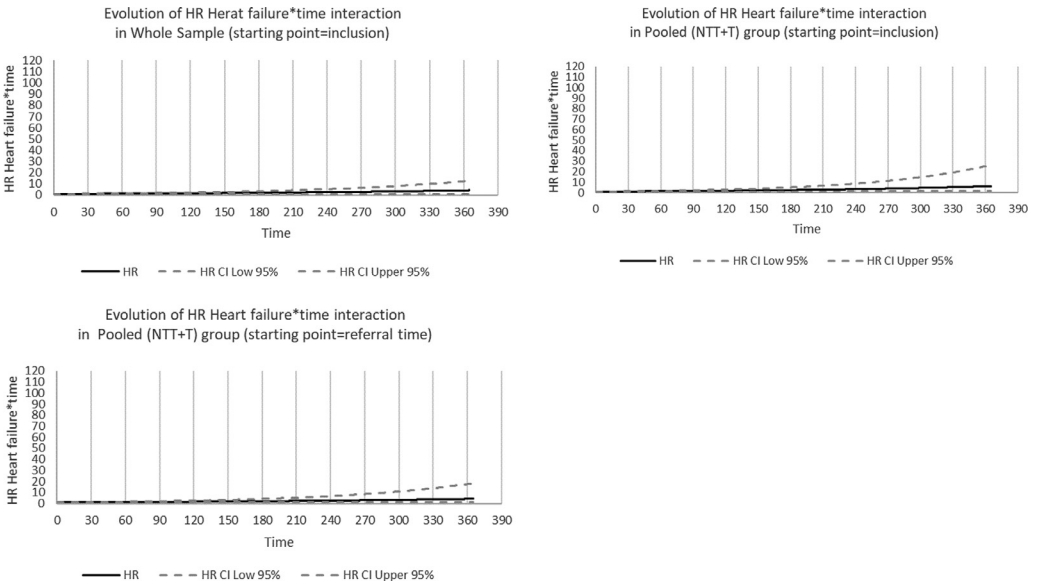

Fig. 3. Evolution over time of Hazard Ratios for the association between heart failure and one-year mortality.

2. Experimental Design, Materials and Methods

2.1. The EI 2008 cohort

2.1.1. Background

We used data from *EI 2008*, a one-year prospective, population based, cohort study of patients with IE [2]. Inclusion criteria in *EI 2008* were: being over 18 years old, living in one of the seven participating French administrative areas (greater Paris, Lorraine, Rhône-Alpes, Franche-Comté, Marne, Ille-et-Villaine and Languedoc- Roussillon), and being admitted to hospital for IE between January 1st 2008 and December 31st 2008. Diagnosis of IE was adjudicated by a team of infectious diseases professionals. Definite cases of IE (Duke criteria modified by Li [3]) were included in the cohort. Patients were followed during one year after inclusion. Baseline and follow-up data were collected on a standardised case report form by trained clinical research assistants. Information on patients' characteristics, IE profiles, treatment and complications were retrieved from hospital medical records. Vital status was assessed from hospital medical records, general practitioners' records or civil registry office 1 year after inclusion, and date of death was collected when appropriate.

All the patients enrolled in the *EI 2008* cohort (497 patients with a definite diagnosis of IE) were considered for our analyses.

2.1.2. Data collection

Patients were divided into three groups: patients admitted to a tertiary hospital (group T), patients admitted to a non-tertiary hospital and secondarily referred to a tertiary hospital (group NTT), and patients admitted to a non-tertiary hospital and not secondarily referred to a tertiary hospital (group NT).

Baseline data consisted of sociodemographic characteristics (age $\geq$70, sex) and medical history data (Charlson comorbidity index $\geq$2, high blood pressure, injection drug use, underlying heart disease, previous IE and implantable cardiac device). Data on IE profile and IE complications were collected during follow-up in hospital stay. IE profile data included clinical characteristics (suspected source of infection, left heart endocarditis, fever and heart failure), microbiological characteristics (Staphylococcal IE), and echocardiographic characteristics (vegetation and perforation). IE complications data consisted of cardiac abscess, septic shock, cerebral haemorrhage, cerebral embolism, vascular phenomena, immunologic phenomena, persistent sepsis despite treatment, and serum creatinine level $\geq$180 µmol/L.

2.2. Secondary analysis of EI 2008 data

2.2.1. Aim of the study

We used data from the *EI 2008* cohort to provide a comprehensive characterisation of referral bias [1]. Referral bias is a type of selection bias that can occur in studies recruiting patients in tertiary hospitals only (mixing patients admitted directly to tertiary hospitals and those referred secondarily to tertiary hospitals, but excluding patients admitted to non-tertiary hospitals and not referred). Studies on rare diseases such as infective endocarditis are particularly prone to referral bias [4–6], a bias which may threaten the validity of prognostic studies' results [7].

2.2.2. Data analyses

The whole sample (pooled (NT+NTT+T) group) represented a population-based recruitment of patients with IE. The pooled (NTT+T) group was used to mimic prognostic studies recruiting patients in tertiary hospitals.

Two different starting points were considered for the follow-up: inclusion (corresponding to the date of first hospital admission) and referral time (corresponding to the date of first admission to a tertiary hospital if any, i.e. used for groups T and NTT only to mimic prognostic studies

based on patients recruited in tertiary hospitals only). Survival time was calculated from the starting point to the date of death or to the date of last follow-up.

All variables mentioned in data collection were evaluated for their potential prognostic impact. Patients with missing data for at least one of these potential prognostic factors were excluded from analyses (after checking that the characteristics of excluded patients did not differ significantly from those of included patients). One patient (patient number 560) was excluded from analyses due to a negative delay between hospital admission and septic shock (covariate introduced in Cox analyses as a time-dependent covariate). As a result, a total of 466 patients with infective endocarditis were included in the Cox analyses (274 in group T (58,8%), 136 in group NTT (29,2%) and 56 in group NT (12,0%)).

Data presented in tables 1 to 6 were obtained through crude and adjusted Cox modelling of 3-month and 1-year survival from IE. For both 3-months and 1-year survival, analyses were performed in five steps:

1/ In the pooled (NT+NTT+T) group, i.e. a population-based sample, using inclusion as the starting point, a stepwise selection (with a significance level for entry (sle) set at 0.20 and a significance level for staying in the model (sls) set at 0.05) was performed to identify prognostic factors
2/ In the pooled (NTT+T), using inclusion as the starting point, covariates identified as prognostic factors in Step 1 were forced into the multivariable model to identify an eventual difference in significance or in the magnitude of HRs
3/ In the pooled (NTT+T) group, using inclusion as the starting point, a stepwise selection (sle=0.20 and sls=0.05) was performed to naively identify prognostic factors
4/ In the pooled (NTT+T) group, using referral time as the starting point, covariates identified as prognostic factors in Step 1 were forced into the multivariable model to identify an eventual difference in the magnitude or significance of their effect
5/ In the pooled (NTT+T) group, using referral time as the starting point, a stepwise selection (sle=0.20 and sls=0.05) was performed to identify prognostic factors using a design prone to referral bias.

Cox models assumptions (Log-linearity assumption and proportional hazard assumption) were checked. In 1-year Cox analyses, high blood pressure, Charlson comorbidity index, heart failure, and vascular phenomena did not meet the proportional hazard assumption and were considered as time-varying covariates (covariate*time interaction). IE complications occurring during the hospital stay (septic shock, cardiac abscess, cerebral embolism, and cerebral haemorrhage) were introduced in the models as time-dependent covariates. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) software.

Ethics Statement

EI 2008 was conducted in accordance with the Declaration of Helsinki. Patients were informed of the study but their written individual consent was not required. *EI 2008* was authorized by the Commission Nationale de l'Informatique et des Libertés (CNIL-DR-2010-219) and registered in ClinicalTrials.gov (NCT03295045).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

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