



## **Impact of referral bias on prognostic studies outcomes: insights from a population-based cohort study on infective endocarditis**

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## Original article

# Impact of referral bias on prognostic studies outcomes: insights from a population-based cohort study on infective endocarditis

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# **Abstract**

## **Purpose**

Prognostic studies derived from samples of patients managed in tertiary hospitals are subject to referral bias. We aimed to characterise this bias using the example of infective endocarditis (IE).

## **Methods**

We analysed data from a French population-based cohort which included 497 patients with IE in 2008. Patients were admitted directly to a tertiary hospital (group T), or admitted to a non-tertiary hospital and referred to a tertiary hospital (group NTT) or not (group NT). We compared patients' characteristics and survival rates and prognostic factors between groups.

## **Results**

Compared to group T (N=291), NTT patients (N=144) were more often males (81.3% *vs* 72.5%,  $p=0.046$ ), injection drug users (9.7% *vs* 4.5%,  $p=0.033$ ), had more frequent surgical indications (78.5% *vs* 64.3%,  $p=0.003$ ). Compared to group NT (N=62), NTT patients were more often males (81.3% *vs* 67.7%,  $p=0.034$ ) and had surgical indications more often (78.5% *vs* 19.4%,  $p<0.001$ ). One-year survival was higher in (NTT+T) patients than in NT patients (73.0% *vs* 56.1%,  $p=0.01$ ). Prognostic factors as well as HR estimates varied across groups.

## **Conclusion**

When derived from samples mixing patients admitted directly and those referred to tertiary hospitals, validity of characteristics description, survival estimates, and HRs is threatened by referral bias.

## **List of abbreviations**

Group T = patients admitted directly to a tertiary hospital

Group NTT = patients admitted to a non-tertiary hospital and later referred to a tertiary hospital

Group NT = patients admitted to a non-tertiary hospital and non-referred to a tertiary hospital

HR = Hazard ratio

IE = Infective endocarditis

IQR = Interquartile range

## Introduction

Referral bias is a concern in studies recruiting patients in tertiary hospitals only, particularly in cohort studies on rare diseases.

Infective endocarditis (IE) is an example of rare but serious disease with in-hospital mortality above 20% (1) and 1-year mortality reaching 30% (2). Accordingly, acute description of survival and unbiased identification of prognostic factors are crucial to prognosis. Most observational studies aiming to describe prognosis in IE and to identify prognostic factors (3–9) are derived from samples of patients managed in tertiary hospitals, combining patients admitted directly and patients referred to tertiary hospitals. Tertiary hospitals offering exclusive services such as valve surgery, referred patients are more likely to present with indications for valve surgery than patients admitted directly to tertiary hospitals (10,11). Such differences might extend to other baseline characteristics, resulting in a selection bias, namely a referral bias (12), which might affect both survival estimates and prognostic factors identification. In addition, patients who are referred to a tertiary hospital also survived until being referred, which might result in better survival estimates for them than for non-referred patients or for patients admitted directly to tertiary hospitals. Accordingly, prognostic studies based on recruitment of IE cases in tertiary hospitals only (mixing referred patients and patients admitted directly to tertiary hospitals) are prone to referral bias.

By allowing access to information on patients usually excluded from prognostic studies (patients admitted to a non-tertiary hospital and not referred to a tertiary hospital during their follow-up), the *EI 2008* population-based cohort study (1) offers an unique opportunity to comprehensively assess internal validity threats related to referral bias in cohort studies. Using the example of IE, we aimed to assess the extent to which prognostic studies recruiting cases in tertiary hospitals only are prone to referral bias, with particular attention paid to its impact on characteristics estimates, survival estimates and prognostic factors identification.

## **Methods**

### ***Design and Setting***

We used data from *EI 2008*, a one-year prospective, population based, cohort study of patients with IE (1). All patients aged  $\geq 18$  years, living in one of the seven participating French administrative areas (greater Paris, Lorraine, Rhône-Alpes, Franche-Comté, Marne, Ile-et-Villaine and Languedoc-Roussillon) and admitted in hospital for IE between January 1<sup>st</sup> –December 31<sup>st</sup> 2008 were included. Diagnosis of IE according to the Duke criteria modified by Li (13) was adjudicated by an expert team, and definite cases of IE were included. Patients were followed during one year after inclusion.

All patients enrolled in the *EI 2008* cohort (497 definite IE cases), were included in the present investigation.

### ***Data collection***

Baseline characteristics consisted of socio-demographic and medical history data. Inclusion was the starting point for follow-up, and was set at the date of first hospital admission. Follow-up data consisted of data collected during hospital stay. Occurrence and date of occurrence (if relevant) of referral to a tertiary hospital were recorded. To assess the impact of referral bias on both survival estimates and identification of prognostic factors, we mimicked a prognostic study recruiting in tertiary hospitals only by using an additional starting point, named referral time, set at the date of first admission to a tertiary hospital if any. Clinical features, microbiological and echocardiographic features, and IE complications were collected during follow-up.

Vital status was collected from medical records or civil registry office one year after inclusion.

Survival time was calculated from the starting point to the date of death. Surviving patients were censored at the date of last follow-up.

### ***Ethics***

This cohort study conforms to the principles outlined in the Declaration of Helsinki. Patients were informed of the study and individual consent was waived, in accordance with French legal standards.

*EI 2008* was authorized by the *Commission Nationale de l'Informatique et des Libertés* (CNIL-DR-2010-219) and registered in ClinicalTrials.gov (NCT03295045).

### ***Statistical analyses***

We considered three groups of patients: patients admitted directly to a tertiary hospital, further identified as “admitted to a tertiary hospital” (group T), patients admitted to a non-tertiary hospital and referred secondarily to a tertiary hospital, further identified as “later referred patients” (group NTT), and patients admitted to a non-tertiary hospital and not secondarily referred to a tertiary hospital, further identified as “non-referred patients” (group NT).

First, we described patients’ characteristics overall and stratified on the three groups, using median and interquartile range for continuous variables, and percentage for categorical variables. We compared these characteristics overall and between groups using Chi-2 (or Fisher exact) tests for categorical variables, and Student (or Mann-Whitney) tests for continuous variables, according to condition of use: group T vs the (NTT+NT) group to assess whether patients admitted to a tertiary hospital differed from patients admitted to a non-tertiary hospital, group NTT vs group NT to assess whether later referred patients differed from non-referred patients, and group T vs group NTT to assess whether patients admitted to a tertiary hospital differed from those later referred.

We estimated 1-month, 3-month, and 1-year survival after inclusion and after referral time, overall and in the three groups (or in groups T and NTT when using referral time as the starting point), using Kaplan Meier estimate. Kaplan Meier estimates were compared using Log-rank tests.

Then, we identified prognostic factors for 3-month and 1-year mortality through Cox modelling in the whole sample (first batch of crude and adjusted models), *i.e.* a population-based sample, using inclusion as the starting point; and then in the (NTT+T) group (second batch of crude and adjusted models), *i.e.* mimicking prognostic cohort studies based on samples recruited in tertiary hospitals only, first using inclusion as the starting point and second using referral time as the starting point. For the first batch of models, a stepwise selection was applied to the variables with a significance level to enter set at 0.20 and significance level to stay set at 0.05. For the second batch of models, covariates

resulting from the selection process of the first batch were forced into the models in order to reveal an eventual difference in the magnitude or in the significance of their effect; and then a stepwise selection was secondarily performed in order to naively identify prognostic factors. Log-linearity assumption was checked for continuous explanatory covariates. Proportional hazard assumption was assessed by plotting Schoenfeld residuals. Charlson comorbidity index, high blood pressure, heart failure, and vascular phenomena did not meet this assumption for 1-year Cox analyses, and were entered as time-varying covariates (covariate\*time interaction) in the corresponding models. IE complications (septic shock, cardiac abscess, cerebral embolism, and cerebral haemorrhage) were considered as time-dependent covariates. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) software.



## Results

### Description of patients' characteristics

Among the 497 patients, 291 patients were admitted to a tertiary hospital (group T), and 206 patients were admitted to a non-tertiary hospital ((NTT+NT) group), of whom 144 were later referred to a tertiary hospital (group NTT) and 62 were not (group NT) (Figure 1).

Patients' characteristics and between-group comparisons are shown in table 1. We found no difference in sociodemographic, medical history, IE clinical, microbiological, and echocardiographic profile, and IE complications between patients admitted to a tertiary hospital (group T) and those who were admitted to a non-tertiary hospital ((NTT+NT) group).

Compared to non-referred patients (group NT), later referred patients (group NTT) were younger (median[IQR] age 64.5[23.0] years in group NTT *vs* 72.5[21.0] years in group NT,  $p=0.001$ ), more often males (81.3% *vs* 67.7%,  $p=0.034$ ), and had less often a history of high blood pressure (44.4% *vs* 62.9%,  $p=0.015$ ). They also had different IE profiles: IE locations ( $p=0.003$ ) and causative microorganisms ( $p=0.035$ ). They presented more often with indications for valve surgery (78.5% *vs* 19.4%,  $p<0.001$ ), such as valve perforation (20.8% *vs* 8.1%,  $p=0.025$ ), severe regurgitation (48.3% *vs* 19.7%,  $p<0.001$ ), and cardiac abscess (27.8% *vs* 6.5%,  $p<0.001$ ). They less frequently presented with contraindications for valve surgery (18.6% *vs* 100.0%,  $p<0.001$ , among patients with indication for valve surgery).

Compared to patients who were admitted to a tertiary hospital (group T), later referred patients (group NTT) were more often males (81.3% in group NTT *vs* 72.5% in group T,  $p=0.046$ ), injection drug users (9.7% *vs* 4.5%,  $p=0.033$ ), had more often echocardiographic abnormalities (97.2% *vs* 91.1%,  $p=0.017$ ) or cerebral haemorrhages (11.8% *vs* 5.8%,  $p=0.029$ ). They also presented more often with indications for valve surgery (78.5% *vs* 64.3%,  $p=0.003$ ).

### Survival estimates

A total of 142 deaths occurred in one year (76 in group T, 39 in group NTT, and 27 in group NT), and 25 patients (5.0%) were lost to follow-up (9 patients in group T, 5 in group NTT, and 1 in group NT).

One-month overall survival estimates were similar whatever the starting point (85.8% using inclusion as the starting point, 85.1% using referral time as the starting point). Three-month (78.0% using inclusion as the starting point vs. 79.3% using referral time), and even more 1-year (70.8% using inclusion as the starting point vs. 75.4% using referral) overall survival were overestimated when using referral time as the starting point instead of inclusion (Table 2).

One-year survival in patients managed in a tertiary hospital at some point ((NTT+T) group) was better ( $p=0.01$ ) than survival in non-referred patients (group NT) (Table 2, Figure 2). One-month, 3-month, and 1-year survival in patients admitted to a tertiary hospital (group T) did not differ from survival in later referred patients (group NTT) whatever the starting point.

### **Identification of prognostic factors**

Considering inclusion as the starting point, we identified nine prognostic factors of 1-year mortality in the whole sample (Table 3): age  $\geq 70$  (HR 2.402[1.653-3.489],  $p<0.001$ ), Charlson comorbidity index  $\geq 2$ \*time (HR 1.008[1.003-1.013],  $p=0.001$ ), high blood pressure\*time (HR 1.006[1.002-1.010],  $p=0.006$ ), heart failure\*time (HR 1.004[1.000-1.007],  $p=0.027$ ), Staphylococcal IE (HR 1.679[1.177-2.395],  $p=0.004$ ), valve perforation (HR 0.545[0.327-0.909],  $p=0.020$ ), septic shock (HR 3.360[2.211-5.104],  $p<0.001$ ), cerebral embolism (HR 2.324[1.556-3.469],  $p<0.001$ ), and serum creatinine level  $\geq 180\mu\text{mol/L}$  (HR 2.780[1.944-3.977],  $p<0.001$ ). These nine covariates were still associated with survival in the sample of patients managed in a tertiary hospital at some point (NTT+T) group) when considering inclusion as the starting point, but with lower HRs as compared to HRs derived from the whole sample for age  $\geq 70$  and septic shock; and higher HRs for serum creatinine level  $\geq 180\mu\text{mol/L}$ . No additional prognostic factor was identified when secondarily performing Cox model using a stepwise selection.

When considering referral time as the starting point and forcing the nine previous covariates into the model, heart failure was no longer associated with survival. The eight other covariates were still

associated with survival but with higher HRs as compared to HRs derived from the whole sample for cerebral embolism and serum creatinine  $\geq 180 \mu\text{mol/L}$ ; and lower HR for age  $\geq 70$  and septic shock.

When performing a stepwise selection, valve perforation and heart failure were no longer identified as prognostic factors of 1-year mortality.

Prognostic factors of 3-months mortality did not differ across groups whatever the starting point considered, but their magnitude of effect varied (e-component 1).

## Discussion

### *Main findings*

Using a cohort of IE patients, we conducted the first comprehensive characterization of referral bias that could threaten the validity of estimates derived from cohort studies recruiting patients in tertiary hospitals only. The sample mixing patients admitted directly to tertiary hospitals and those later referred led to referral bias affecting patients' characteristics estimates, survival and Hazards Ratios for prognostic factors, jeopardizing any attempt of predictive score development.

### *Impact of referral bias on patients' characteristic estimates*

Some studies on IE have described the impact of referral bias on patients' characteristics estimates (10–12,14–17), finding out similar between group differences for valve surgery (10,11,16), echocardiographic abnormalities (11), and IE complications (10). However, these studies restricted their comparisons to IE patients admitted to tertiary hospitals *vs* those who were later referred (group T *vs* group NTT in our study). None of these studies have included patients who were admitted to a non-tertiary hospital and not referred to a tertiary hospital (group NT in our study), probably due to uncollected data for these patients. Yet, considering non-referred patients might be critical to comprehensively assess the impact of referral bias.

Compared to non-referred patients (group NT), later referred patients (group NTT) were younger, more often males, and presented more often indications for valve surgery. These differences might be explained by the ESC guidelines recommending referring IE cases with indications for valve surgery to tertiary centres (18). In addition, tricuspid IE was more frequent in later referred patients, probably related to a more frequent injection drug use (19). Other locations of IE were also more frequently observed in later referred patients, suggesting that relatively rare locations of IE required more often the expertise offered exclusively in tertiary centres. Similarly, IE due to microorganisms other than *Staphylococcus* or *Streptococcus*, also requiring a higher level of expertise, were more frequently observed in later referred patients than in non-referred patients.

No differences were found in terms of socio-demographic characteristics, medical history, IE profile, and IE complications between patients admitted to tertiary hospitals (group T) and patients admitted to non-tertiary hospitals (pooled (NTT+NT) group). Patients admitted to tertiary hospitals (group T) presented similar characteristics as compared to patients admitted to non-tertiary hospitals ((NTT+NT) group), reflecting a community-based recruitment in both types of hospitals. These similarities might pertain to the French health system specifics: in France, patients can go to the hospital of their choice and usually choose the nearest one. Whether this hospital is a tertiary hospital or not might not be considered in the balance.

Accordingly, mixing referred IE cases (group NTT) and cases admitted to a tertiary hospital (group T), thus neglecting non-referred cases, might bias baseline characteristics estimates.

### ***Impact of referral bias on survival estimates***

Recruiting cases in tertiary hospitals usually leads to set the starting point of survival time at the time of tertiary hospital admission (referral time). In our study, setting the starting point at referral time led to overestimate overall survival from three months and further on as compared to using inclusion (first hospital admission) as the starting point. This might be explained by the exclusion of non-referred patients with poorer prognostic from these estimations. This might also be explained by greater chances to undergo interventions that have proven effective, such as valve surgery (20) or benefiting from the expertise offered in tertiary hospitals. To support this hypothesis, our results showed that 1-year survival in patients managed in a tertiary hospital at some point ((NTT+T) group) was better than survival in non-referred patients (group NT). From a public health perspective, these differences in survival ( $NT < (NTT+T)$ ) might raise concerns about eventual differences in patient management across the settings. However, a comparison of the time spans between the main milestones of patients' management (hospital admission, first blood culture, start of antibiotic therapy, first echocardiography) across groups did not highlight any difference that might explain the observed survival differences (data not shown). Accordingly, differences in patients' characteristics, especially

age and contraindication to surgery, were more likely to explain the observed between groups survival differences.

One-month, 3-month, and 1-year survival estimates in patients admitted to a tertiary hospital (group T) did not differ from survival in later referred patients (group NTT) whatever the starting point. These results are consistent with the literature on referral bias in IE (11,12). Several hypotheses can explain these results. First, referred patients need to survive until being referred, in other words patients with more serious IE might be dead before referral. Second, as described by *Paltiel et al.* (21) about referral bias in lymphoma studies, there is a paradox concerning survival: On the one hand, later referred patients have better chances of survival than non-referred patients because they are younger and in better health than those who non-referred; on the other hand, later referred patients may be the most severe cases (requiring a specialised team); thus hiding survival differences.

#### ***Impact of referral bias on assessment of prognostic value of IE patients' characteristics***

Prognostic outcomes identified in our study were consistent with those previously described in the literature. The effect of age (4,6,22), Charlson comorbidity index (3,23), heart failure (22), staphylococcal IE (4,6,7,24), septic shock (22,23), cerebral embolism (24,25), and high serum creatinine level (5,24) on survival in IE have already been described. The protective effect of valve perforation on 1-year survival from IE was unexpected. Patients suffering from a valve perforation had less often a medical history of underlying heart disease than those who did not have a valve perforation, potentially explaining their better survival. This result could also be explained by residual confounding from unmeasured covariates.

The impact of referral bias on identification of IE prognostic factors associated with 3-month mortality from IE was weak: No difference was found in the prognostic factors identified between the two samples ((NTT+T) group vs whole sample) in all Cox models. No difference was found in prognostic factors of 1-year mortality identified between the two samples when considering inclusion as the starting point for analyses. However, when using referral time as the starting point in the pooled (NTT+T) group, two of the previous prognostic factors were no longer associated with survival,

meaning that studies based on tertiary hospital recruitment might miss identification of factors of actual prognostic value. An impact on HRs magnitude of effect should also be mentioned, mainly on 1-year survival when comparing HRs obtained in the whole sample and HRs obtained when using referral time as the starting point in the (NTT+T) group. Selection bias occurs in prognostic studies when the association between exposure and outcome differs between study participants and non-participants (26). A different prevalence of exposure in study participants versus non-participants is not sufficient to cause selection bias with respect to effect measures; this exposure must also be associated with the outcome (27). In our study, non-referred patients (group NT) were older, presented more often with a history of high blood pressure, and had a higher Charlson comorbidity index (though this result failed to reach statistical significance) as compared to later referred patients (group NTT). As mentioned earlier, age, high blood pressure, and Charlson comorbidity index are also associated with survival. Consequently, referral bias can be considered a selection bias threatening the validity of prognostic value estimates in cohort studies of IE patients recruited in tertiary hospitals only.

### **Socio-economic status, health coverage and referral to tertiary hospitals**

In France, tertiary hospitals are public hospitals located in major regional cities. Patients from group T were therefore more likely to be living in (or close to) these regional affluent areas (28,29). Patients from groups NT and NTT were first admitted to public or private hospitals. Those first admitted to public non-tertiary hospitals were more likely to live further from major cities. Patients from groups NT and NTT admitted to private hospitals (35 patients) could either be living in major cities or further away, but were likely to come from a higher socio-economic background. However, because data on individual socio-economic status level were not collected in *EI 2008*, we could not assess whether tertiary hospital recruited patients from higher socio-economic background than non-tertiary hospitals, which might have explained part of the better survival observed in patients from T group.

In addition, all French residents get access to a universal health coverage through the statutory health insurance (SHI) (30,31). Public hospital fees are fixed by the State, and more than two-thirds of these

fees are covered by the SHI. More than 95% of the population is covered by a non-for-profit private health insurance covering the remaining fees (32). The level of coverage for hospital care is approximately the same for everyone (31). Referral to tertiary hospitals was therefore unlikely to be influenced by differences in health insurances plans, and by extension unlikely influenced by socioeconomic status.

### **Implications for future research**

A population-based recruitment must be preferred to a recruitment in tertiary hospitals, especially when the main focus is patients' characteristics description or prognosis estimation; otherwise results might be biased.

### **Limitations**

First, our data were quite old (2008), but as indications for valve surgery in IE remained similar since then, referral practices are not likely to have evolved either. Moreover, despite improvements in surgical procedures, survival rates in our study are consistent with those reported in recent studies on IE (2). Accordingly, our conclusion on referral bias is unlikely affected by this time span since 2008.

Secondly, multiple comparisons made between groups might have resulted in first order risk inflation. However, confronting the part of our results that could be confronted to the existing literature led to similar conclusions about referral bias.

Lastly, the date of hospital admission, used as the starting point in our analyses, is not a perfect indicator of the beginning of IE. Other starting points, such as first day of antibiotic therapy, might have been relevant but they would not have led to less biased estimations of length of IE.

### **Conclusion**

Descriptive results from studies on patients recruited in tertiary hospitals only must be interpreted carefully as referral bias may jeopardize the findings, especially the description of patients' characteristics and survival estimates. The validity of HR values of prognostic factors might also be threatened by referral bias; though further studies are needed to strengthen this conclusion.



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### **Conflicts of interest**

The authors declare that they have no conflicts of interest.

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2 Table 1: Characteristics of the 497 patients with Duke-Li definite Infective Endocarditis (IE) according to group

	<b>Group T N=291 (58.6%)</b>	<b>Group NTT N=144 (29.0%)</b>	<b>Group NT N=62 (12.5%)</b>	<b>Overall p*</b>	<b>T vs (NTT+NT) p*</b>	<b>NTT vs NT p*</b>	<b>T vs NTT p*</b>
<b><u>Socio-demographic</u></b>							
<b>Age (years), median (IQR)</b>	63.0 (22.0)	64.5 (23.0)	72.5 (21.0)	<b>0.003</b>	0.252	<b>0.001</b>	0.672
<b>Male, n (%)</b>	211 (72.5)	117 (81.3)	42 (67.7)	0.063	0.239	<b>0.034</b>	<b>0.046</b>
<b><u>Medical history</u></b>							
<b>Charlson Comorbidity index, median (IQR)</b>	1.0 (3.0)	1.0 (3.0)	2.0 (2.0)	0.178	0.603	0.127	0.743
<b>High blood pressure, n (%)</b>	131 (45.0)	64 (44.4)	39 (62.9)	<b>0.028</b>	0.273	<b>0.015</b>	0.910
<b>Diabetes mellitus, n (%)</b>	67 (23.0)	28 (19.4)	18 (29.0)	0.317	0.856	0.130	0.395
<b>Dialysis, n (%)</b>	7 (2.4)	2 (1.4)	2 (3.2)	0.676	1.000	0.585	0.724
<b>Injection drug use, n (%)</b>	13 (4.5)	14 (9.7)	2 (3.2)	0.057	0.122	0.156	<b>0.033</b>
<b>Underlying heart disease (HD), n (%)</b>				0.590	0.728	0.337	0.652
Prosthetic valve	61 (21.0)	34 (23.6)	9 (14.5)				
Previously known HD without prosthetic valve	73 (25.1)	39 (27.1)	19 (30.6)				
No previously known HD	157 (54.0)	71 (49.3)	34 (54.8)				
<b>Previous IE, n (%)</b>	16 (5.5)	14 (9.7)	2 (3.2)	0.131	0.310	0.156	0.102
<b>Cardiac implantable electronic device (PM</b>	40 (13.7)	22 (15.3)	4 (6.5)	0.216	0.716	0.080	0.667

	<b>Group T N=291 (58.6%)</b>	<b>Group NTT N=144 (29.0%)</b>	<b>Group NT N=62 (12.5%)</b>	<b>Overall p*</b>	<b>T vs (NTT+NT) p*</b>	<b>NTT vs NT p*</b>	<b>T vs NTT p*</b>
<b>or ICD), n (%)</b>							
<b><u>IE profile</u></b>							
<b><u>Clinical characteristics</u></b>							
<b>Suspected source of infection, n (%)</b>				0.607	0.885	0.221	0.549
Community	210 (73.9)	107 (74.8)	45 (76.3)				
Healthcare-related, acquired in hospital	65 (22.9)	34 (23.8)	11 (18.6)				
Healthcare-related, not acquired in hospital	9 (3.2)	2 (1.4)	3 (5.1)				
<b>Left heart endocarditis, n (%)</b>	233 (80.1)	115 (79.9)	51 (82.3)	0.915	0.887	0.690	0.959
<b>Location of IE, n (%)</b>				.**	0.377	<b>0.003</b>	0.307
Aortic	91 (31.3)	48 (33.3)	15 (24.2)				
Mitral	98 (33.7)	44 (30.6)	29 (46.8)				
Aortic and mitral	39 (13.4)	19 (13.2)	2 (3.2)				
Tricuspid	22 (7.6)	16 (11.1)	3 (4.8)				
Bilateral	5 (1.7)	4 (2.8)	5 (8.1)				
Pacemaker	14 (4.8)	10 (6.9)	2 (3.2)				
Other location	2 (0.7)	0 (0.0)	0 (0.0)				

	<b>Group T N=291 (58.6%)</b>	<b>Group NTT N=144 (29.0%)</b>	<b>Group NT N=62 (12.5%)</b>	<b>Overall p*</b>	<b>T vs (NTT+NT) p*</b>	<b>NTT vs NT p*</b>	<b>T vs NTT p*</b>
Unknown	20 (6.9)	3 (2.1)	6 (9.7)				
<b>Fever, n (%)</b>	246 (85.1)	127 (89.4)	51 (82.3)	0.317	0.501	0.157	0.217
<b>Heart failure, n (%)</b>	100 (34.4)	53 (36.8)	15 (24.2)	0.204	0.753	0.078	0.616
<b>NYAH class III or IV, n (%)</b>	60 (22.1)	32 (25.0)	8 (14.3)	0.270	0.919	0.105	0.527
<b><u>Microbiological characteristics</u></b>							
<b>Microorganisms, n (%)</b>				0.089	0.308	<b>0.035</b>	0.466
<i>Streptococcus</i>	143 (49.1)	61 (42.4)	36 (58.1)				
<i>Staphylococcus</i>	97 (33.3)	59 (41.0)	24 (38.7)				
Other microorganisms or $\geq 2$ Microorganisms	34 (11.7)	16 (11.1)	1 (1.6)				
No microorganism identified	17 (5.8)	8 (5.6)	1 (1.6)				
<b>Staphylococcal IE</b>	97 (33.3)	59 (41.0)	24 (38.7)	0.269	0.112	0.761	0.118
<b><u>Echocardiographic characteristics</u></b>							
<b>Echocardiographic abnormalities, n (%)</b>	265 (91.1)	140 (97.2)	56 (90.3)	<b>0.048</b>	0.084	0.069	<b>0.017</b>
<b>Vegetation, n (%)</b>				0.382	0.882	0.121	0.933
No vegetation	37 (12.7)	18 (12.5)	7 (11.3)				
$\leq 15$ mm	127 (43.6)	59 (41.0)	36 (58.1)				



	<b>Group T N=291 (58.6%)</b>	<b>Group NTT N=144 (29.0%)</b>	<b>Group NT N=62 (12.5%)</b>	<b>Overall p*</b>	<b>T vs (NTT+NT) p*</b>	<b>NTT vs NT p*</b>	<b>T vs NTT p*</b>
>15mm	73 (25.1)	40 (27.8)	13 (21.0)				
Unknown size of vegetation	54 (18.6)	27 (18.8)	6 (9.7)				
<b>Valve perforation, n (%)</b>	55 (18.9)	30 (20.8)	5 (8.1)	0.080	0.586	<b>0.025</b>	0.632
<b>Prosthesis dehiscence, n (%)</b>	9 (14.8)	10 (29.4)	1 (11.1)	0.179	0.168	0.407	0.087
<b>Severe regurgitation, n (%)</b>	113 (39.2)	69 (48.3)	12 (19.7)	<b>0.001</b>	0.916	<b>&lt;0.001</b>	0.074
<b><u>IE complications</u></b>							
<b>Cardiac abscess, n (%)</b>	57 (19.6)	40 (27.8)	4 (6.5)	<b>0.002</b>	0.629	<b>&lt;0.001</b>	0.054
<b>Septic shock, n (%)</b>	46 (15.8)	23 (16.0)	13 (21.0)	0.598	0.622	0.386	0.965
<b>Cerebral embolism, n (%)</b>	60 (20.6)	35 (24.3)	9 (14.5)	0.279	0.842	0.116	0.381
<b>Cerebral haemorrhage, n (%)</b>	17 (5.8)	17 (11.8)	4 (6.5)	0.082	0.072	0.244	<b>0.029</b>
<b>Other embolism, n (%)</b>	97 (33.3)	53 (36.8)	15 (24.2)	0.211	0.940	0.078	0.473
<b>Vascular phenomena, n (%)</b>	137 (47.1)	74 (51.4)	27 (43.5)	0.535	0.668	0.302	0.397
<b>Immunologic phenomena, n (%)</b>	39 (13.6)	14 (10.0)	5 (8.2)	0.350	0.161	0.688	0.286
<b>Persistent sepsis despite treatment, n (%)</b>	30 (10.3)	19 (13.2)	4 (6.5)	0.371	0.761	0.228	0.370
<b>Serum creatinine level <math>\geq 180 \mu\text{mol/L}</math>, n (%)</b>	76 (26.6)	50 (35.2)	15 (25.0)	0.139	0.179	0.156	0.065
<b>Indication for valve surgery, n (%)</b>	187 (64.3)	113 (78.5)	12 (19.4)	<b>&lt;0.001</b>	0.416	<b>&lt;0.001</b>	<b>0.003</b>

	<b>Group T</b> <b>N=291 (58.6%)</b>	<b>Group NTT</b> <b>N=144 (29.0%)</b>	<b>Group NT</b> <b>N=62 (12.5%)</b>	<b>Overall</b> <b>p*</b>	<b>T vs</b> <b>(NTT+NT)</b> <b>p*</b>	<b>NTT vs NT</b> <b>p*</b>	<b>T vs NTT</b> <b>p*</b>
<b>Contraindication for valve surgery, n (%)</b>	43 (23.0)	21 (18.6)	12 (100.0)	<b>&lt;0.001</b>	0.492	<b>&lt;0.001</b>	0.366

3 ICD: implantable cardioverter defibrillator PM: pacemaker NYHA: New York Heart Association

4 Group T= admitted to a tertiary hospital, group NTT= later referred to a tertiary hospital, group NT= non-referred patients

5 \* Chi-2 or Fisher exact test for categorical variables; Student or Mann-Whitney tests for continuous variables

6 \*\* Fisher exact test could not be performed

7

8 Table 2: Between groups comparison of patients' survival, considering inclusion or referral time as the starting point

	Starting point = inclusion (I)			Starting point = referral time (II)			Starting point = inclusion (I)				Starting point = referral time (II)
	N***	%	Standard error	N	%	Standard error	Overall <sup>§</sup> p**	Group (NTT+T) vs NT p**	Group T vs (NTT+NT) p**	Group T vs NTT p**	Group T vs NTT p**
<b>1-month survival</b>							0.79	0.76	0.70	0.97	0.26
Overall*	478	85.8	0.02	435	85.1	0.02					
Group (NTT+T)	416	85.6	0.02	435	85.1	0.02					
Group T	291	86.3	0.02	291	86.3	0.02					
Group NTT	125	84.0	0.03	144	82.4	0.03					
Group NT	62	87.1	0.04	-	-	-					
<b>3-month survival</b>							0.40	0.18	0.51	0.88	0.78
Overall*	491	78.0	0.02	435	79.3	0.02					
Group (NTT+T)	429	79.0	0.02	435	79.3	0.02					
Group T	291	79.1	0.02	291	79.1	0.02					
Group NTT	138	78.9	0.03	144	79.0	0.03					
Group NT	62	70.9	0.06	-	-	-					
<b>1-year survival</b>							<b>0.03</b>	<b>0.01</b>	0.22	0.91	0.53
Overall*	497	70.8	0.02	435	75.4	0.02					
Group (NTT+T)	435	73.0	0.02	435	75.4	0.02					
Group T	291	73.2	0.03	291	73.2	0.03					
Group NTT	144	72.6	0.04	144	77.8	0.03					
Group NT	62	56.1	0.06	-	-	-					

9 Group T= admitted to a tertiary hospital, group NTT= later referred to a tertiary hospital, group NT= non-referred patients, group (NTT+T) = patients managed in a tertiary  
10 hospital at some point, group (NTT+NT) = patients first admitted to a non-tertiary hospital

11

12 Table 3: Comparison of factors associated with 1-year mortality according to sample selection and starting point

Whole sample starting point=inclusion N=466					Pooled (NTT+T) group starting point=inclusion N=410					Pooled (NTT+T) group starting point=referral time N=410							
Model 1					Model 1					Model 2							
n	HR	95% CI	p*	n	HR	95% CI	p**	HR	95% CI	p*	n	HR	95% CI	p**	HR	95% CI	p*
<b><u>Socio-demographic</u></b>																	
<b>Age</b>			<b>&lt;0.001</b>					<b>&lt;0.001</b>					<b>&lt;0.001</b>				
< 70	285	ref	-		261	ref	-		ref	-		261	ref	-		ref	-
≥70	181	2.402	1.653-3.489		149	2.193	1.460-3.293		2.193	1.460-3.293		149	2.310	1.520-3.511		2.317	1.526-3.518
<b><u>Medical history</u></b>																	
<b>Charlson Comorbidity index<sup>1</sup></b>			<b>0.001</b>					<b>0.005</b>					<b>0.005</b>		<b>0.036</b>		
<2	252	ref	-		230	ref	-		ref	-		230	ref	-		ref	-
≥ 2	214	1.008	1.003-1.013		180	1.007	1.002-1.012		1.007	1.002-1.012		180	1.005	1.000-1.010		1.006	1.001-1.011
<b>High blood pressure<sup>1</sup></b>			<b>0.006</b>					<b>0.007</b>					<b>0.007</b>		<b>0.005</b>		
No	245	ref	-		225	ref	-					225	ref	-		ref	-
Yes	221	1.006	1.002-1.010		185	1.006	1.002-1.011		1.006	1.002-1.011		185	1.009	1.003-1.016		1.009	1.003-1.016
<b><u>IE profile</u></b>																	
<b>Heart failure<sup>1</sup></b>			<b>0.027</b>					<b>0.017</b>					<b>0.017</b>		0.081		
No	307	ref	-		266	ref	-		ref	-		266	ref	-			
Yes	159	1.004	1.000-1.007		144	1.005	1.001-1.009		1.005	1.001-1.009		144	1.004	1.000-1.008			
<b>Staphylococcal IE</b>			<b>0.004</b>					<b>0.015</b>					<b>0.015</b>		<b>0.020</b>		
No	297	ref	-		263	ref	-		ref	-		263	ref	-		ref	-
Yes	169	1.679	1.177-2.395		147	1.634	1.102-2.423		1.634	1.102-2.423		147	1.618	1.079-2.426		1.633	1.092-2.443
<b>Valve perforation</b>			<b>0.020</b>					<b>0.047</b>					<b>0.047</b>		<b>0.038</b>		
No	381	ref	-		330	ref	-		ref	-		330	ref	-			
Yes	85	0.545	0.327-0.909		80	0.574	0.332-0.992		0.574	0.332-0.992		80	0.543	0.305-0.966			

Whole sample starting point=inclusion N=466					Pooled (NTT+T) group starting point=inclusion N=410					Pooled (NTT+T) group starting point=referral time N=410								
Model 1					Model 1					Model 2								
	n	HR	95% CI	p*	n	HR	95% CI	p**	HR	95% CI	p*	n	HR	95% CI	p**	HR	95% CI	p*
<b>IE complications</b>																		
<b>Septic shock<sup>2</sup></b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>			<b>&lt;0.001</b>				<b>&lt;0.001</b>			<b>&lt;0.001</b>
No	390	ref	-		345	ref	-		ref	-		345	ref	-		ref	-	
Yes	76	3.360	2.211-5.104		65	2.991	1.874-4.773		2.991	1.874-4.773		65	2.847	1.754-4.621		2.766	1.721-4.445	
<b>Cerebral embolism<sup>2</sup></b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>			<b>&lt;0.001</b>				<b>&lt;0.001</b>			<b>&lt;0.001</b>
No	369	Ref	-		321	ref	-		ref	-		321	ref	-		ref	-	
Yes	97	2.324	1.556-3.469		89	2.266	1.452-3.535		2.266	1.452-3.535		89	2.499	1.581-3.949		2.551	1.615-4.029	
<b>Serum creatinine level ≥180 μmol/L</b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>			<b>&lt;0.001</b>				<b>&lt;0.001</b>			<b>&lt;0.001</b>
No	333	Ref	-		291	ref	-		ref	-		291	ref	-		ref	-	
Yes	133	2.780	1.944-3.977		119	2.882	1.941-4.278		2.882	1.941-4.278		119	3.085	2.053-4.634		3.055	2.031-4.594	

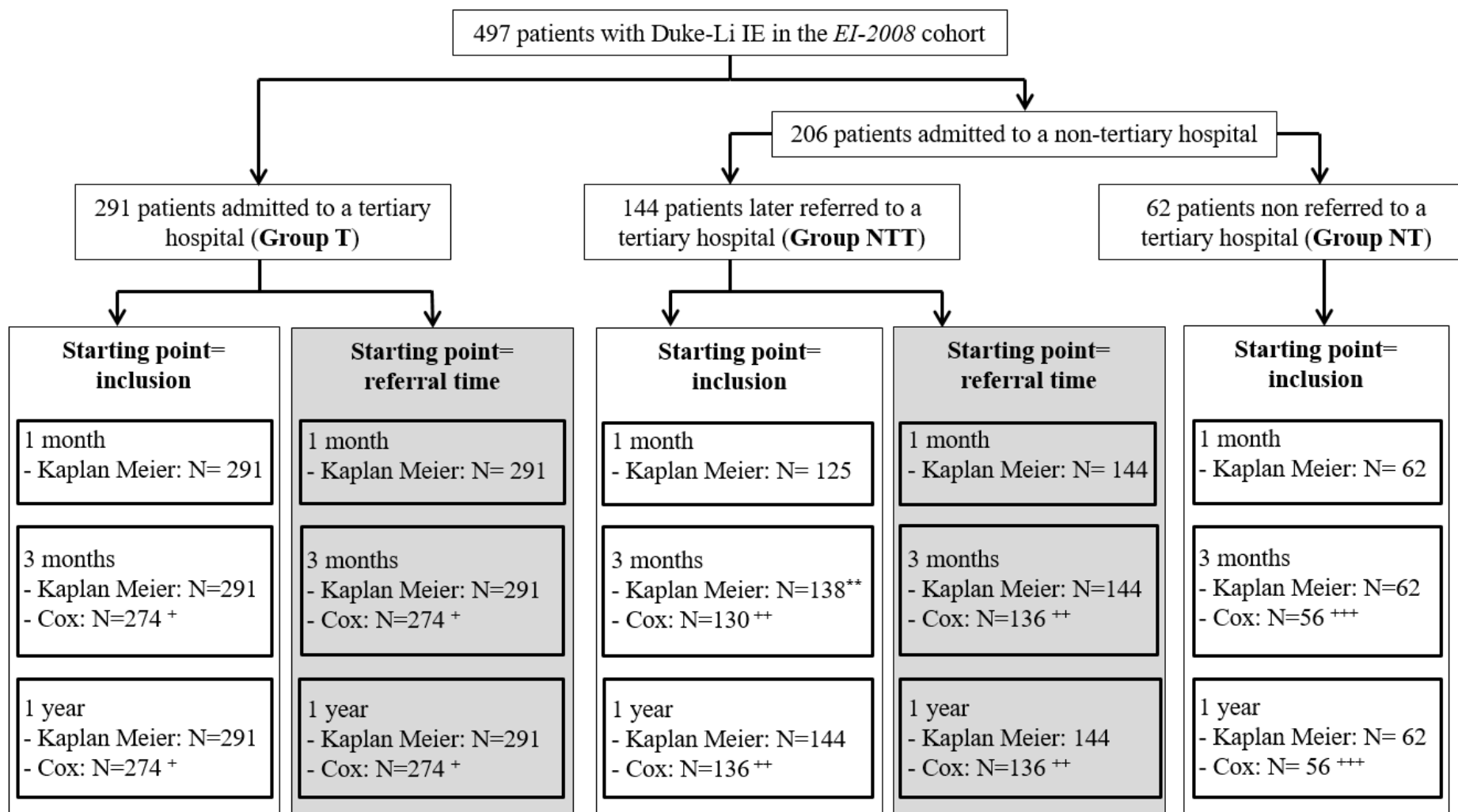
13

14    HR= hazard ratio                    CI= confidence interval                    \* Multivariate Cox regressions were performed. Stepwise selection, sle=0.20, sls=0.05

15    \*\* Covariates resulting from the selection process in the whole sample were forced into the model

16    <sup>1</sup> time-varying covariate (covariate\*time interaction)                    <sup>2</sup> time-dependent covariate

17

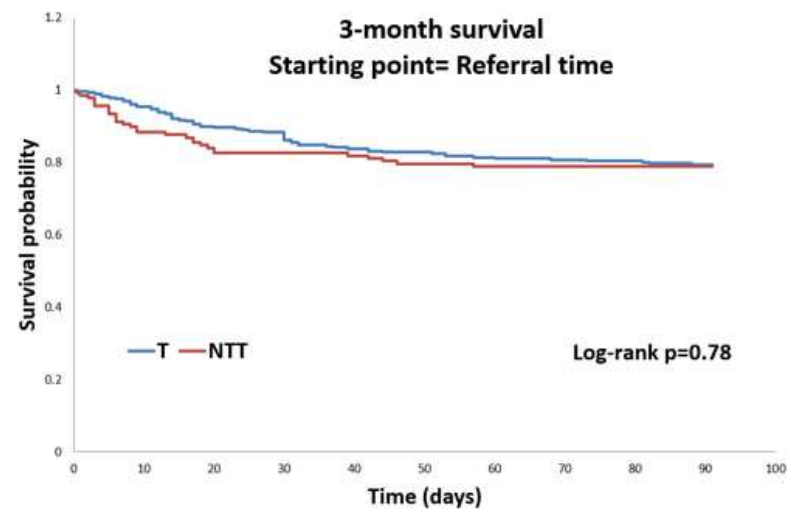
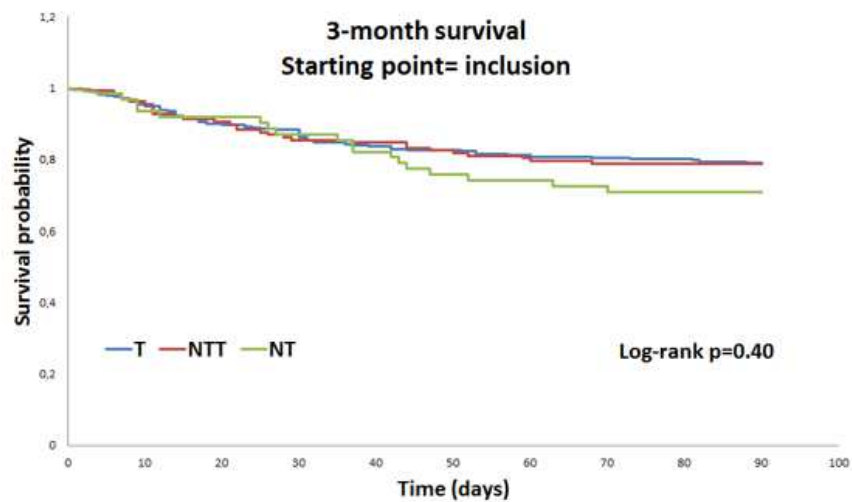
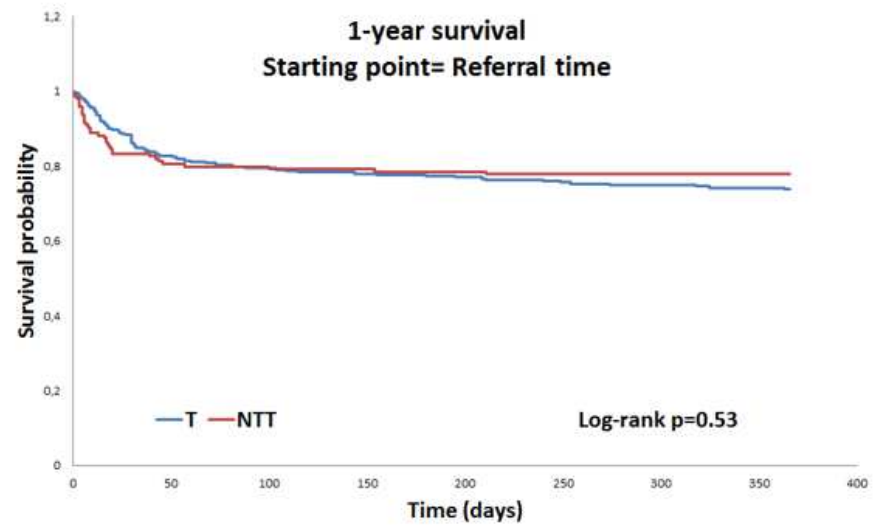
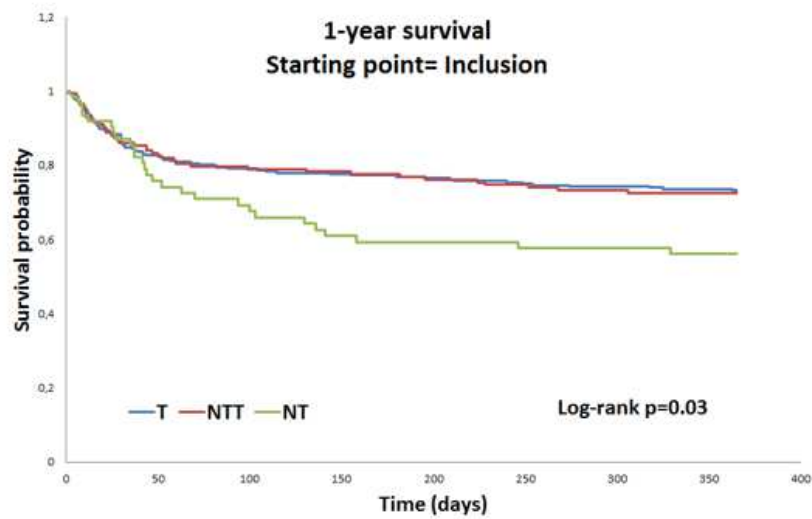


18

19 Figure 1: Flowchart of *EI 2008* patients included in characterization of referral bias analyses

20 <sup>+</sup> Exclusion of patients due to missing data on eligible variables for Cox models (N=17)

- 21    \* Exclusion of patients not referred yet at 1 month (N=19)
- 22    \*\* Exclusion of patients not referred yet at 3 months (N=6)
- 23    ++ Exclusion of patients due to missing data on eligible variables for Cox models (N=8)
- 24    +++ Exclusion of patients due to missing data on eligible variables for Cox models (N=6)
- 25



26

27 Figure 2: 1-year and 3-month survival curves



28     Group T = admitted to a tertiary hospital, Group NTT = later referred to a tertiary hospital, Group NT = non referred patients

29