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Frequency and predictors of decisions to change goals of care after acute ischemic stroke

Cover title: Ischemic stroke and change in goals of care

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Abstract

Background and purpose

Little is known about the factors leading to a change in goals of care (CGC) in acute ischemic stroke (AIS) patients. Our aim was to analyze the proportion and outcome of such patients and identify medical predictors of a CGC during acute hospitalization in a comprehensive stroke unit.

Methods

We retrospectively reviewed all AIS patients over a 13-year period from the prospectively constructed Acute STroke Registry and Analysis of Lausanne (ASTRAL). We compared patients with a CGC towards maximizing quality rather than quantity of life during the acute hospital phase to all other patients, and identified associated clinical and radiological variables using logistic regression analysis.

Results

A CGC decision was taken in 440/4264 (10.3%) consecutive AIS patients during their acute hospitalization. The most powerful acute phase predictors of a CGC were transit through the intensive care unit, older age, pre-existing disability, higher stroke severity, and initial decreased level of consciousness. Adding subacute phase variables, we also identified active oncological disease, fever, and poor recanalization as predictors. Of the CGC patients, 76.6% died in the stroke unit and 1.0% of other patients, and 30.5% of patients with a CGC received a palliative care consultation. For patients with a CGC who did not die during acute hospitalization, 8.1% were transferred to nursing homes, 6.8% to acute care hospitals, and 6.4% to palliative care centers. At 12 months, 93.6% of patients with CGC had died, compared with 10.1% of non-CGC patients.

Conclusions

Over three-quarters of AIS patients with CGC died in hospital, but less than a third received a palliative care consultation. The identified clinical and radiological predictors of a CGC may allow physicians to initiate timely the decision-making process for a possible CGC and involvement of a palliative care consultation team.

Key words

Palliative care, ASTRAL registry, acute ischemic stroke, acute and subacute phase predictors

Non-standard Abbreviations and Acronyms

CGC = Change in goals of care

AIS = Acute Ischemic Stroke

ASTRAL = Acute STroke Registry and Analysis of Lausanne

mRS = modified Rankin Score

DNAR = Do-Not-Attempt to Resuscitate order

NIHSS = National Institutes of Health Stroke Scale

ASPECTS = Alberta Stroke Program Early CT Score

PAD = Peripheral Artery Disease

Introduction

Stroke is one of the leading causes of death and adult-onset disability worldwide (1) ~~and in Switzerland~~. The health care system is now facing a growing number of elderly stroke patients with a higher burden of pre-stroke disability and comorbidities. Questions regarding a change in goals of care (CGC) from a life-sustaining to a comfort-oriented approach in acute ischemic stroke (AIS) patients, will therefore become more important, focusing on the quality rather than quantity of life. Discussion of a CGC is part of the palliative care process, which was granted a formal specialty status in the United Kingdom and the United States (2), and the increasing number of guidelines (2, 3)(6) has the potential to influence the way all health care professionals will work to improve the quality of life in severe diseases and end-of-life situations (4, 5). Irrespective of the decision on the goal of care, it is recommended that palliative medicine should be offered to any seriously ill patient including stroke patients (2, 3, 6), given that consideration of quality of life is essential.

Decision making in CGC rests, as with all treatment goals, on two normative criteria: first, the medical indication for providing a certain type of care, defined as "the appropriateness of a therapeutic or diagnostic measure in the patient's concrete clinical situation, in light of the best available evidence" (4). Second, if life-sustaining treatment is judged as medically indicated, the treatment has also to be agreed upon by the patient's autonomous value judgement.

The determination of the appropriate goals of care for patients with AIS should include the possibility of a CGC. Despite a growing literature on CGC and palliative care for AIS patients (2, 4, 5), little is known about the medical predictors for transition to comfort-oriented care and the outcome of the patients. After investigating end-of-life symptoms in AIS patients (7), we aimed to analyze here, the medical predictors of CGC decisions and the outcome of such decisions on AIS patients in a tertiary stroke center.

Methods

We reviewed the prospectively constructed Acute STroke Registry and Analysis of Lausanne (ASTRAL) for all AIS admitted to our institution's stroke unit and/or intensive care unit within 24 hours between 01/2003 and 12/2016 (8). A large range of parameters were analyzed retrospectively: demographics, pre-stroke disability estimated by modified Rankin score (mRS), medical history, cardiovascular risk factors, comorbidities (according to Elixhauser and Charlson indexes (9)), current medication, clinical deficits and time metrics in the acute stroke phase. We described clinical assessment, indications for revascularization treatments, and neuroimaging in the acute and subacute phase in the supplementary material. The rest of the acute stroke management and secondary prevention of ASTRAL patients followed European Stroke Organization and American Stroke Association guidelines at the time of hospitalization. Discharge disposition of survivors and time and cause of any death were recorded at discharge, then at 3 months in the outpatient clinic, and through a structured telephone interview at 12 months by mRS-certified personnel. Causes of death were classified as stroke-related or-unrelated, and vascular or non-vascular.

Patients or their legal representatives and the neurologist in charge addressed the proposal of a CGC during the acute hospitalization based on clinical variables such as initial course, comorbid conditions, pre-stroke disability, prior patient directives, or declared or presumed wishes of the patient. According to Swiss law and professional guidelines, a patient's representatives have the right to decide on the patient's behalf in patients lacking decision-making capacity as long as they do not seem to go against the presumed will of the patient (5). Any CGC decision was registered in the patient's medical record and in ASTRAL. Patients are then prescribed a do-not-attempt resuscitate order (DNAR) if not already done so at admission, and this information entered in the medical record (but not in ASTRAL).

Once a CGC was adopted, the treatment goal shifted towards maximizing quality of life rather than prolonging it. Neurological and cardiovascular drugs were discontinued except for cardiac failure or antiepileptic drugs for preventing discomfort. Analgesics, including parenteral opioids, sedatives and anxiolytics were prescribed on an as-needed basis. Nasogastric feeding was usually stopped and oral nutrition only given upon patient request, even in the presence of a risk of broncho-aspiration. The stroke unit's physician-in-charge requested a palliative care consultation if the family, nurses, or physicians had specific palliative care questions, or if they had doubts about the patient's comfort. Information on the frequency of these consultations was obtained after comparing the patients with a CGC with the list of in-hospital consultations maintained by the palliative care service (list available for the years 2009 – 2016).

For statistical analysis, ordinal and continuous data are presented as medians with interquartile range (IQR) and categorical data as absolute counts and percentage. In the direct comparison analyses, we performed univariate comparisons between groups of all pertinent variables and expressed them as odds ratios (ORs) with confidence interval (CI). We conducted multivariate analyses using logistic regression models. Variable selection for the multivariate analyses were performed via backward elimination with a threshold equal to 0.157. We started with the full model, eliminated the least significant variable and fitted a new model. This procedure was repeated until all p-values were smaller than the threshold. Results are expressed as ORs with CI and associated p-values to quantify and test the significance of the strength of association.

Kaplan-Meyer survival curves were constructed for "free of a CGC" and "free of death" during the hospital phase and up to 12 months. For analyses of 12-month outcome, we included patients up to 12/2015 in order to have a near complete dataset.

The Vaud Cantonal Commission on Ethics in Human Research authorized the use of ASTRAL for scientific purposes.

Results

We analyzed 4264 consecutive patients from ASTRAL for this study, with a median age of 73.6 years (44.2% female). A CGC was decided for 440 patients (10.3%); they had a median age of 81.1 years, and 54% were female. Table 1 summarizes other patient baseline data. For the years 2009 - 2016 where the information was recorded, 89/292 (30.5%) of patients with a CGC received a palliative care consultation.

Timing of a CGC

The median time from admission to a CGC decision was 3 days (IQR 6), with a peak at 2 days (figure 1); about two-thirds of the decisions were made within five days (23.2% within 2 days, 63% within 5 days and 74.7% within 7 days). The median time between hospitalization and death for patients with a CGC was eight days (IQR 13). In 3.9% of cases, the CGC decision was reversed during the hospital stay towards life-prolongation.

Predictors for adopting a CGC

CGC patients were older compared to the control group, had a higher proportion of pre-stroke-disability, a higher stroke severity from the National Institutes of Health Stroke Scale (NIHSS) and more comorbidities and risk factors (table 1). In the subacute phase, the difference in NIHSS between the two groups was even higher, and symptomatic intracranial hemorrhage and ischemic mass effect were higher in the univariate analysis (table 1 and supplementary table 1).

In the multivariate analysis of factors associated with a CGC in the acute hospital phase, we found eleven acute phase predictors, the most powerful being transit through intensive care. Pre-stroke disability, peripheral artery disease (PAD), higher age, higher NIHSS, and decreased level of consciousness on admission also showed strong association. Additional associations are listed in table 2.

When adding subacute variables to the above analysis, higher admission NIHSS was replaced by higher 24-hour NIHSS, and PAD by coronary artery disease. Additional factors also emerged, such as active oncological disease, subacute fever and non-recanalization of cervico-cerebral arteries. The area under the receiver operating characteristic curve (AUC) for the acute phase model was 0.906, and 0.938 for the subacute phase.

Patient fate and causes of death

The overall in-hospital mortality for AIS patients over the study period was 8.8%, with 89.6% of them undergoing a CGC. In CGC patients, the proportion of in-hospital death was 76.6% (337/440), while in the others 1.0% (39/3824). The causes of in-hospital and post-hospital deaths were more often related to stroke in the CGC group (supplementary table 2).

AIS survival in CGC patients showed a steep decline over the first 20 days (figure 2), compared to a slow and linear decline in patients without a CGC.

Status at hospital discharge

The median duration of hospitalization in patients with a CGC was 8 days (IQR: 12), and for other patients 9 days (IQR: 7). In patients who had a CGC, 23.3% (103) left the stroke unit alive. Of these, 34.3% were discharged to a nursing home, 29.1% to another acute care hospital, 27.1% to a specialized palliative care or hospice institution, 3.9% to a rehabilitation institution and 4.9% were sent to specialized hospice care (supplementary table 3) and 75 (72.8%) of them died within a year. Among all patients with a CGC, 404/440 (91.8%) and 412/440 (93.6%) had died by the 3- and 12-month follow-ups, respectively. In the patients without an in-hospital CGC decision, 181/3824 (4.7%) and 385/3824 (10.1%) had died by 3 and 12 months, respectively. The proportion of patients alive with severe disability (mRS 4 or 5) at 3 and 12 months was higher in the CGC group (table 1).

Discussion

We found that 10% of consecutive AIS patients from a tertiary stroke unit had a CGC during their acute hospitalization, with a median time of 3 days to the decision. The population with a CGC was older, had more pre-stroke disability, and higher stroke severity. Other medical predictors of CGC were transit through intensive care, decreased level of consciousness on admission, arterial occlusions on acute imaging, and several factors in the subacute phase. Approximately one-third (30.5%) of CGC patients received a palliative care consultation in the stroke unit.

Our observed CGC rate of 2.4% of all AIS patients within 48 hours was similar to the 3% in the ischemic stroke patients of Prabhakaran's analysis (10). Of interest, our overall 10% in-hospital CGC rate is similar to the current combined rates of thrombolysis and thrombectomy therapies in in Europe (11), but far less research and effort goes into palliative care in AIS patients despite two problems of similar magnitude.

Our palliative care consultation rate of 30.5% in CGC patients (and 2.1% in all AIS patients) was rather high taking into consideration the short period before death in many, and the unavailability of these consultations at night and on weekends. In a similar study, Singh et al. also showed that less than 5% of all AIS patients receive a palliative care consultation (12). Our observations and current recommendations (2, 3)(6) support the need for specialized palliative services in hospitals caring for acute stroke patients.

Our time-to-CGC decision of three days is in line with the existing literature (13-15). This seems an appropriate length when considering the occasional requirement to observe the initial clinical course and the need of the family to adapt to the new situation. In the one-third of patients where a decision was taken after seven days, there might be a potential to initiate CGC dialogue earlier if multiple predictors of a CGC are present.

So far in AIS patients, there is little data concerning medical predictors of a CGC. A US-study (14) identified advanced age, greater stroke severity, left-sided stroke, intra-arterial thrombolysis, and atrial fibrillation as independent predictors in dysphagic patients. In our sample, the strongest predictor in the acute phase was transit through the intensive care unit, suggesting severe stroke and circulatory or respiratory instability. Other strong predictors were a pre-stroke disability, higher age and NIHSS on admission, a decreased level of consciousness, and high blood glucose, confirming our previous findings of poor prognosis (16-18). We also confirmed that radiological parameters such as a lower ASPECTS score and cerebrovascular occlusions were associated with a worse outcome, again acknowledging other reports (16, 19).

In the subacute phase (table 2), the 24-hour NIHSS replaced admission NIHSS as predictor, which suggests that the observation of the clinical course over 24 hours seems to be a useful option before making a CGC decision in some patients. In addition, metastatic malignant disease became a strong predictor in the subacute phase, as did PAD, replacing coronary artery disease in the acute phase. As in previous studies (20), hyperthermia became a predictor of CGC decision only in the subacute phase. Finally, non-recanalization of arterial occlusions at 24 hours was associated with subsequent CGC, as shown in other publications (21).

Not surprisingly, many of our predictors of CGC were similar to predictors of poor long-term outcome after AIS, including death (22, 23). Still, intensive care unit transit, cerebrovascular occlusive arterial pathology, absence of arterial recanalization at 24 hours do not usually figure in the predictive scores. Interestingly, onset-to-arrival time, sex, stroke mechanism, psychiatric comorbidities and insurance status, all associated with early stroke mortality (24, 25), were not associated with a CGC decision.

Both in our analysis and the Norwegian study (15), the interquartile range between the CGC decision and death varied widely. This finding should be communicated to the next of kin so that they are prepared for the possibility of a long period before death. Of the 10.3% of patients

that had a CGC, 93.6% had died by 12 months (76.6% during the acute hospital phase and 17.0% thereafter). On the other hand, only 1.0% of patients without CGC died during the hospital phase (and 9.1% over the next 12 months). This low death rate in patients without CGC suggests that most in-hospital deaths after stroke are foreseeable, allowing for the initiation of a CGC review in most. In addition, the high proportion of in-hospital CGC decisions allowed the majority (89.6%) of all patients who died in-hospital to shift to treatments emphasizing quality of life rather than suffering from life-prolonging measures. Indeed, CGC decisions were reversed to life-prolonging measures because of unanticipated clinical improvement during the hospital course in only 4% situations; all these patients then went to rehabilitation centers.

A criticism of our findings is the 'self-fulfilling prophecy' (26) of do-not-resuscitate orders followed by death, as discussed by other authors (27). On the other hand, an appropriate CGC decision may not only prevent an unwanted prolongation of life, but also allow for improvement in quality of life in a situation where further life-sustaining treatments appear unwarranted.

Most in-hospital deaths in both CGC and control groups were directly related to stroke (93% in the CGC cohort and 81% in the control group). It is not surprising that this number is lower in the control cohort because many of these deaths were due to unexpected, internal events.

Of the patients with a CGC who left the hospital alive (23%), only a minority received further care in a palliative care institution (27%) or at home with palliative care (5%). A higher proportion of discharge to specialized palliative care would be desirable.

Limitations of this study are its retrospective, observational nature in a mostly elderly Caucasian population from a comprehensive stroke center including about 25% referred patients. Also, the important proportion of in-hospital strokes (about 8 %) with more comorbidities increases the proportion of CGC-eligible patients. Third, we did not record data on dysphagia, medical

complications, DNAR status before admission, religion, prior patient directives (28), ethical attitudes of patients and proxies.

In summary, our study identifies multiple factors that allow physicians to recognize the need for a discussion with the patient or their representatives on a CGC. If the medical indication for a CGC is unequivocal ('futile care' situation), the decision should be communicated empathically to the patient and family (4).

Better knowledge of the predictors and early path of stroke patients with a CGC may help the stakeholders in acute stroke care to avoid unproductive treatments and allow for a timely introduction of palliative care. Further research is needed regarding the validity of our findings and the decision-making process in AIS patients and the relevance of these findings for AIS patients admitted to hospitals without stroke units (29).

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Disclosures

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The other authors report no conflict of interest.

Supplementary Materials

Online tables I-II

TABLES AND FIGURES

Table 1: Key baseline data of the study population. Results are displayed as absolute counts and percentages for categorical variables and median with interquartile range (IQR) for continuous variables.

Variable	Overall population included	Patients with CGC (N=440)	Control group (N=3824)	OR (95% CI)
Age	73.6(20.6)	81.1(14.4)	72.6(20.7)	1.05(1.05–1.06)*
Female sex	1882(44.2%)	238(54.0%)	1644(43.0%)	1.56(1.28–1.90)*
Pre-existing mRS > 2	443(10.4%)	120(27.6%)	323(8.5%)	4.11(3.24–5.22)*
Vascular risk factors (pre-existing or newly diagnosed)				
Hypertension	3060(71.9%)	328(74.7%)	2732(71.5%)	1.18(0.94–1.48)
Diabetes	797(18.7%)	88(20.1%)	709(18.6%)	1.1(0.86–1.41)
Smoking	972(23.1%)	57(13.2%)	915(24.3%)	0.48(0.36–0.64)*
Atrial fibrillation	1254(29.5%)	210(47.8%)	1044(27.4%)	2.43(1.99–2.97)*
Comorbidities				
Active oncological disease	223(5.3%)	33(7.6%)	190(5%)	1.55(1.06–2.28)*
Renal failure	594(14%)	116(26.4%)	478(12.6%)	3.49(1.98–3.15)*
Psychiatric disorder	570(13.6%)	58(13.2%)	512(13.7%)	0.96(0.72–1.29)
Prehospital and in-hospital treatment times				

Variable	Overall population included	Patients with CGC (N=440)	Control group (N=3824)	OR (95% CI)
Onset-to-door time (minutes)	192(529.5)	152.5(396.3)	196(536.5)	1(1–1)*
Clinical and radiological characteristics on admission				
NIHSS	6(11)	19(9.75)	6(9)	1.17(1.19–1.19)*
Decreased vigilance	498(11.9%)	167(39.5%)	331(8.8%)	6.75(5.39–8.45)*
ASPECTS	10(2)	8(5)	10(1)	0.74(0.71–0.77)*
Significant intracranial arterial pathology^	2037(57.5%)	282(88.7%)	1755(54.4%)	6.56(4.5–9.34)*
Intensive care unit admission at any time in current hospitalization	376(8.9%)	116(26.7%)	260(6.9%)	4.95(3.87–6.34)*
Symptomatic hemorrhage (ECASS-II < 7 days)	100(2.5%)	48(13.2%)	52(1.4%)	10.62(7.05–15.98)*
Symptomatic ischemic mass effect < 7 days	49(4.5%)	21(19.3%)	28(2.8%)	8.21(4.48–15.05)*
In-hospital death	376(8.8%)	337(76.6%)	39(1.0%)	316.45(215.33–465.05)*

Variable	Overall population included	Patients with CGC (N=440)	Control group (N=3824)	OR (95% CI)
mRS 4 or 5 in patients alive at 12 months	355(10.2%)	9(32%)	346(10%)	3.19(1.5-6.83)*
Death at 12 months	797(18.6%)	412(93.6%)	385(10.1%)	131.43(88.37–195.5)*

* Significant OR. ^Significant pathology in intracranial arteries within the ischemic territory on admission imaging

mRS = modified Rankin score. NIHSS = National Institutes of Health Stroke Scale. ASPECTS= Alberta Stroke Program Early CT Score. CTP = Computed Tomography Perfusion. ECASS-II = European Cooperative Acute Stroke Study-II.

Table 2: Multivariate analysis of significant factors associated with a CGC during the acute hospitalization phase. Results are displayed as odds ratios with 95% confidence intervals.

Analysis of acute phase data only	Odds ratio	95% CI
Intensive care unit transit	3.18	2.00–5.06
Pre-stroke mRS>2	2.29	1.43–3.66
CTA pathology in relevant area*	1.93	1.18–3.17
Peripheral artery disease	1.91	1.03–3.54
Decreased level of consciousness on admission	1.76	1.16–2.69

NIHSS on admission (per point)	1.12	1.09–1.16
Admission glucose level (per mmol/l)	1.12	1.06–1.19
Age (per year)	1.06	1.05–1.08
Admission CRP level (per mg/l)	1.01	1.00–1.01
Admission hemoglobin level (per g/l)	0.99	0.98–1.00
ASPECTS on non-contrast CT	0.81	0.76–0.87
Analysis of acute and subacute phase data		
Metastatic cancer	6.61	2.22–19.72
Prestroke mRS > 2	5.12	2.81–9.34
CTA pathology in relevant area*	2.95	1.52–5.60
Documented coronary artery disease	2.23	1.35–3.79
Subacute temperature (per °Celsius)	1.64	1.15–2.35
NIHSS at 24 hours	1.22	1.18–1.26
Admission glucose level (per mmol/l)	1.10	1.02–1.19
Age (per year)	1.05	1.03–1.07
Delta creatinine**(per umol/l)	1.01	1.00–1.02
Subacute diastolic blood pressure (per mmHg)	0.98	0.96–0.99
Recanalization at 24 hours	0.35	0.15–0.70

*Significant pathology in intracranial arteries within the ischemic territory on admission imaging

**Calculated as: subacute creatinine–acute creatinine

Figure 1: Time from admission to CGC decision.

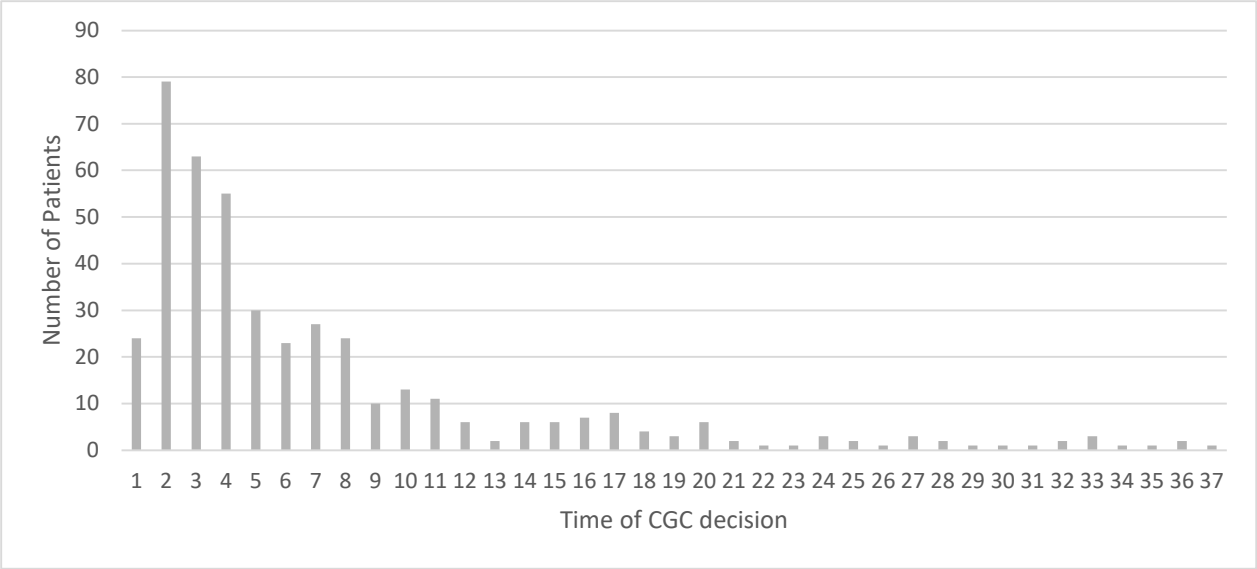
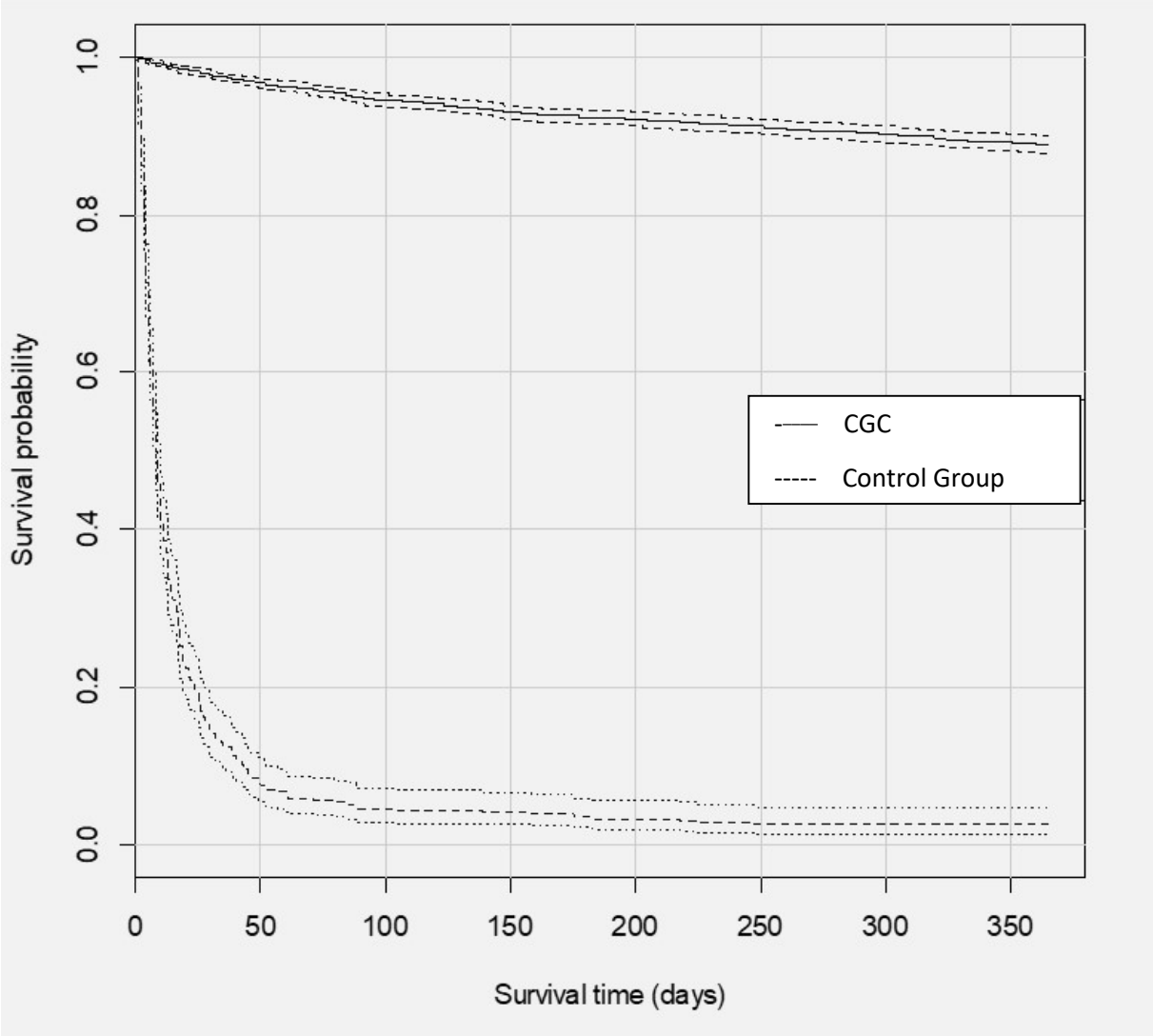


Figure 2: Survival curves of patients with a CGC and the rest of the AIS patients



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