Survival Analysis and Influence of the Surgical Aggression of a Cohort of Orthopedic and Trauma Patients in a Non-controlled Spread COVID-19 Scenario

Fernando Corella (✉ fernando.corella@gmail.com)

Hospital Universitario Infanta Leonor: Hospital Infanta Leonor <https://orcid.org/0000-0002-8044-8416>

Roberto Rosales

GECOT

David Guzman

Hospital Universitario Infanta Leonor: Hospital Infanta Leonor

Miguel Cañones

Hospital Universitario Infanta Leonor: Hospital Infanta Leonor

Ricardo Larrainzar-Garijo

Hospital Universitario Infanta Leonor: Hospital Infanta Leonor

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Abstract

Background: During the coronavirus disease pandemic, determining the impact of elective and urgent orthopedic and trauma surgeries (OTS) on the infection rate and mortality probability can guide the preparations for next waves. The purpose of this paper was to do a survival analysis in a cohort of non-infected OTS patients and explaining the effect of different grades of surgical aggression.

Methods: This is an observational study of 184 patients who underwent OTS in the month before the halt of surgical activities, before implementation of special measures, and high rate of transmission. Crude risk of infection, infection rates, survival and hazard function analysis, and Cox regression and Fine-Gray models for explaining the effect of aggression and inflammation (groups of surgery).

Results: The crude risk of COVID-19 diagnosis was 14.13% (95%CI: 9.83%–19.90%). The total incidence rate (IR) was 2.67 (1000 person-day) (95%CI: 1.74–3.91). At the end of the follow-up, there was a 94.42% chance of surviving 76 days or more after OTS. The differences in survivor curves by surgery groups were statistically significant and established that Group of surgery 4 presented a lower survival function. The age adjusted for group of surgery, high blood pressure and respiratory history was one of the best model to explain the association with the mortality by COVID-19 (HR: 1.111, CI95%: 1.005-1.228; SHR: 1.111, CI95%: 1.046-1.177)

Conclusions: There is an infection risk after OTS similar to the general population in a community transmission/area; the grade of aggression does not influence this rate. The survival probability is extremely high if patients were not previously infected. Mortality is higher if the group was susceptible to a higher aggression and inflammation grade; however, age adjusted for confounders as groups of surgery, high blood pressure and respiratory history are associated with mortality.

Background

On March 11, 2020, the World Health Organization (WHO) declared the new coronavirus disease 2019 (COVID-19) as a global pandemic. As of May 2020, COVID-19 was spread globally(1). During this first and second waves (that is currently ongoing), Spain has been one of the countries with a higher number of cases and Madrid one of the most affected regions(2).

In the course of these months, due to the changes in hospital infrastructure, cessation of elective and urgent orthopedic and trauma surgery (OTS) has occurred, as many hospital reached the grade 3 COVID-19 occupancy score(3). However, between the waves and in a future, the restauration of a normal orthopedic health care, should occur. That is why, understanding the risk of virus transmission and mortality after performing elective and urgent (OTS) in non-infected patients, in a community with high levels of COVID-19 transmission is essential. It is also indispensable to know the influence of the grade of the surgical aggression to these risks.

There are few reports looking at the risks of infection after performing elective and urgent (OTS), in a community with high levels of COVID-19 transmission. A few studies have analyzed mortality and reported a high rate,(3)(4)(5); however, most of the patients in these studies were already infected or in the incubation period.

The aim of this research was to analyze the risk of infection and perform a survival analysis in a cohort of healthy patients who underwent OTS during a non-controlled spread COVID-19 scenario – before any control measures were taken when the first wave just begun.

The results of the study could be used as a guide for decision-making between waves when elective or trauma surgeries need to be introduced again and detect which patient and type of surgery has the lowest and higher risk.

Methods

Study Design

This observational study, with an ambispective cohort design(6), adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist(7). Patients who underwent OTS from February 13 to March 13, 2020, constituted the study cohort. Once the study population was defined in a retrospective manner, the cohort was followed prospectively till May 5, 2020.

Setting

This study was carried out at the Hospital Universitario Infanta Leonor, located in the south-east side of Madrid City, Spain, which covered a target population of 305,262 patients. The hospital was classified as a grade 3 COVID-19 occupancy(3). On March 13, 2020, the occupancy rate reached 202%, and the hospital was declared a “100% COVID-19 hospital” – no other activity medical or surgical apart from the treatment of COVID-19 patients could be carried out.

Eligibility criteria.

We included all patients who underwent OTS in the month before the halt of surgical activities. In this period, the state of “alert” had not been declared; thus, special protection for patients or professional recommendations were not established, but the rate of transmission was already high. ¶ We decided to choose this period as the surgical activity was completely normal, but the transmission rate was really high (so this is the worst-case scenario) and can mimic periods between waves or when a new one is about to begin.

Patients were recruited by phone called by MC and DG. Prior to the phone interview, patients were asked for their consent to participate in the study.

Data collection.

General data of patients were obtained from the hospital database. Only patients who were admitted at the hospital had all their outcome data recorded from the electronic medical record. For the remaining patients, outcomes were confirmed over a structured phone call interview.

Ethics. The study strictly followed the ethical principles of biomedical research and was approved by the Ethics Committee of the hospital (R-026-20).

Participants

The inclusion criteria were pre-anesthetic assessment approval (no suspicion of COVID-19) and patients older than 18 years of age. The exclusion criteria was patients who did not provide consent to participate in the study.

Variables and Data sources

The primary outcomes of the study were diagnosis of COVID-19 and deaths from COVID-19.

Case definitions were classified as recommended by the Spanish Ministry of Health(8) and WHO(9). The independent and potential confounders were: “Age”, “Sex”, “Body Mass Index” (BMI), “High Blood Pressure” (HBP), “Diabetes” (DM), “History of Respiratory disease” (RespHist), “History of Cardiological disease” (CardiolHist), “History of Kidney disease” (RenalHist), “American Society of Anesthesiologist Physical Status Classification System” (ASA), and “Group of Surgery”.

“Group of surgery” (GS) variable was based on the grade of aggression and inflammation. Four different groups were established based on the location of the surgery and the grade of the surgery considering the NICE guideline(10) Table 1.

Table 1

Groups of Surgery based on the location of the surgery and aggression and inflammation grade.

Groups of Surgery
Group 1: soft tissue and arthroscopic procedures in small joints (foot, ankle, hand and wrist).
Group 2: bone and arthroplasty procedures in small joints
Group 3: soft tissue and arthroscopic procedures in big joints (elbow, shoulder, knee and hip).
Group 4: bone and arthroplasty procedures in big joints.

Statistical Analysis

Crude rates.

Crude risks and Risk Ratio (RR) of COVID-19 diagnosis were determined by case definition and by group of surgery, and their 95% confident interval (CI) were calculated. Crude incidence rates (person-day) and crude incidence rate ratio (IRR) of COVID-19 diagnosis by GS and their 95% CI were obtained.

Survival and hazard function analysis

Survival function of the entire cohort was analyzed by Kaplan-Meier (K-M)(11) and life-table actuarial methods. Survival and failure functions by GS were analyzed by K-M and by competing risk model(12). Comparison of the K-M survival curves by GS was assessed by the Mantel-Cox log rank test(13), the Breslow test(14), and the Tarone-Ware test(15), which followed the chi-squared distribution establishing as null hypothesis (H_0) the equality of survivor functions and a level of significance (α) of 0.05.

Quality of follow-up

The distribution of the frequencies of the different states (Alive, Dead, Lost) at the end of the follow up was calculated. The follow-up period for the different states at the last observation in the cohort was analyzed as another indicator of the quality of the follow-up; moreover, the minimum, maximum, mean, median, 25th, and 75th percentiles were assessed by the different states at the end of the follow-up.

Multivariate survival analysis for measuring the effect.

1.- Selection of IV.

All IVs were assessed by Univariate Cox Regression analysis and those IVs which presented a $P \leq 0.20$ could be considered as confounder (17). BMI and ASA variables were excluded based on the univariate analysis (**complete data in additional file 6**). "RespHist" ($P = 0.989$), with a non-significant hazard ratio was included in the multivariate analysis because of its theoretical importance. The final IVs selected were: "Age", "Group of Surgery", "HBP", "DM", "RespHist", "CardiolHist", and "RenalHist".

2.- Maximum model (MMax).

Based on previous publications(16), the variable "Age" was selected as the main predictor variable and the rest of the IVs as possible confounders. The final reference model (MMax) was built up based on the confounders and their interaction with the predictor variable.

3.- Assessment of the Interactions.

The interactions were assessed by a Chunk test, which compared the reference model (MMax) with the model without the interactions (MMaxNoInteract) based on the likelihood ratio statistic that followed the chi-squared distribution with a df equal to k (number of IVs) minus the number of interactions, establishing ($\alpha = 0.05$) (**complete data in additional file 6**).

4.- Assessment of the confounders.

Following the Maldonado and Greenland recommendations(17), confounders were assessed not by statistical test but based on the change in their effect or hazard ratio (HR) being less than 10% compared with the reference model. The final models were compared by the user command of Stata “confound”(18) (**complete data in additional file 6**).

5.- Final model assessment.

The final selected models adjusted by confounders were analyzed by a Cox Regression model and by Fine-Gray Regression model(19–21) for competing risks, which showed the effect based on the sub hazard ratio (SHR).

Results

Only one patient was not enrolled in the study population because verbal consent was not obtained. One hundred and eighty-four patients were recruited. No patient was lost to follow-up. Demographic data and the distribution of the IVs are shown in Table 2.

Table 2
Demographic data and independent variables distribution.

	Entire Cohort		Small Joints (soft tiss./arthros.)		Small Joints (bone or arthrop.)		Big Joints (soft tiss./arthros.)		Big Joints (bone or arthrop.)	
Age, N, mean (SD)	184	60,04 (18,81)	44	53,39 (16,34)	54	52,80 (15,21)	21	52,72 (15,18)	65	72,92 (17,57)
Sex male, n/N	81/184	44.02%	22/44	50.00%	18/54	33.33%	13/21	61.90%	28/65	43.08%
High blood preassure, n/N	74/184	40.22%	13/44	29.55%	16/54	29.63%	5/21	23.81%	40/65	61.54%
DM, n/N	24/184	13.04%	6/44	13.64%	1/54	1.85%	3/21	14.29%	14/65	21.53%
History of Renal disease, n/N	11/184	5.98%	0/44	0.00%	0/54	0.00%	0/21	0.00%	11/65	16.92%
History of Cardiological disease, n/N	26/184	14.13%	2/44	4.55%	3/54	5.56%	1/21	4.76%	20/65	30.77%
History of Respiratory disease, n/N	38/184	20.65%	5/44	11.36%	14/54	25.93%	3/21	14.29%	16/65	24.62%
BMI, N, mean (SD)	175	28,53 (5,64)	42	28,52 (5,84)	52	28,42 (6,26)	20	29,38 (4,65)	61	28,34 (5,33)
ASA Classification N										
I	27/184	14.67%	9	33.33%	9	33.33%	3	11.11%	6	22.22%
II	119/184	64.67%	31	26.05%	42	35.29%	16	13.45%	30	25.21%
III	32/184	17.39%	3	9.38%	3	9.38%	2	6.25%	24	75%
IV	6/184	3.26%	1	16.67%	0	0.00%	0	0.00%	5	83.33%

The total number of missing values was only 0.41% (9/184 missing values in the BMI); thus, we assure that the missing values did not affect the results(22).

The quality of the follow-up was classified as excellent with no lost at the end of the last observation and a mean follow-up time of 32.8 days.

The crude risk of COVID-19 diagnosis in the entire cohort and according to the four different GS are shown in Table 3. The relative risks (RRs) of COVID-19 diagnosis by GS, taking group 1 as reference, were not significant independently, including or not the suspected cases (**complete data in additional file 1**).

Table 3

Risks of COVID-19 diagnosis. RRs: relative risks. (*) In case of zero event, the RR was computed with a constant continuity correction ($k = 0.5$).

a) Risk of COVID diagnosis by group of surgery								
	Cases	N	Risk	Wilson (95% Conf. Interval)		RR	(95% CI)	
Small Joints (soft tiss./arthros.)	8	44	18.18%	9.51%	31.96%	1	NA	NA
	7	54	12.96%			0.71	0.28	1.81
Small Joints (bone or arthrop.)				6.42%	24.42%			
Big Joints (soft tiss./arthros.)	0	21	0.00%	0.00%	15.46%	0,12*	0.01	1.99
Big Joints (bone or arthrop.)	11	65	16.92%	9.72%	27.82%	0.93	0.41	2.13
Total	26	184	14.13%	9.83%	19.90%			
b) Risk of COVID diagnosis (only probable and confirmed cases) by group of surgery								
	Cases	N	Risk	Wilson (95% Conf. Interval)		RR	(95% CI)	
Small Joints (soft tiss./arthros.)	1	44	2.27%	0.40%	11.81%	1	NA	NA
Small Joints (bone or arthrop.)	2	54	3.70%	1.02%	12.54%	1.63	0.15	17.38
Big Joints (soft tiss./arthros.)	0	21	0.00%	0.00%	15.46%	0,68*	0.03	16.07
Big Joints (bone or arthrop.)	9	65	13.85%	7.46%	24.27%	6.09	0.80	46.40
Total	12	184	6.52%	3.77%	11.05%			

The total incidence rate (IR) and the crude IR (1000 person-day) of COVID-19 diagnosis are shown in Table 4. There were no statistical differences in the incidence rate ratio (IRR) taking GS 1 as reference.

Table 4

Incidence rate (IR) and incidence rate ratio (IRR) of COVID-19 diagnosis. (*) one-sided, 97.5% confidence interval for zero event.

IR and IRR of COVID diagnosis by group of surgery								
	person-time	Failures	IR (1000 person-day)	Poisson- Exact (95% Conf. Interval)		IRR	Exact (95% CI)	
Small Joints (soft tiss./arthros.)	2254	8	3.55	1.53	6.99	1	.	.
Small Joints (bone or arthrop.)	2984	7	2.35	0.94	4.83	0.66	0.24	1.82
Big Joints (soft tiss./arthros.)	1031	0	0	0	3.58*	0		
Big Joints (bone or arthrop.)	3469	11	3.17	1.58	5.67	0.89	0.36	2.22
Total	9738	26	2.67	1.74	3.91			

Of the 26 patients with COVID-19 diagnosis, 16/184 (8.7%) presented with mild symptoms, stayed at home, and did not require any specific drug treatment and 5/184 (2.72%) were admitted in the hospital because of a more severe disease, but

survived. There were 7/184 (3.80%) deaths in the entire cohort, 5 of them (2.72%) were deaths that fit the criteria of COVID-19 deaths and 2 (1.09%) were deaths not caused by COVID-19 (**complete data in additional file 2**).

The cumulative survival probabilities of the entire cohort with the Kaplan-Meier method and with the actuarial method are shown in Table 5 (**complete data in additional file 3**). At the end of the follow-up, there was a 94.42% chance of surviving 76 days or more after OTS. The actuarial method showed that most of the COVID-19 deaths occurred during the first month and a half after surgery. The cumulative probability of survival after 60 days and up to 75 days was 0.957.

Table 5
Survival function of entire cohort.

a) Survival function. Kaplan -Meier method. Entire Cohort						
Time	Beg.	Deaths	Net Lost	Survival probability	[95% Conf. Int.]	
2	184	1	0	0.9946	0.9621	0.9992
19	183	1	1	0.9891	0.9572	0.9973
30	180	0	1	0.9891	0.9572	0.9973
31	179	1	0	0.9836	0.9500	0.9947
40	178	0	4	0.9836	0.9500	0.9947
41	174	1	1	0.9780	0.9423	0.9917
44	164	0	15	0.9780	0.9423	0.9917
60	84	0	2	0.9780	0.9423	0.9917
70	37	0	8	0.9780	0.9423	0.9917
71	29	1	11	0.9442	0.8172	0.9838
76	10	0	10	0.9442	0.8172	0.9838
b) Survival function. Actuarial Method. Entire Cohort						
Interval days	Beg.	Deaths	Lost	Survival probability	[95% Conf. Int.]	
0 15	184	1	0	0.9946	0.9621	0.9992
15 30	183	1	2	0.9891	0.9571	0.9973
30 45	180	2	29	0.9771	0.9402	0.9914
45 60	149	0	65	0.9771	0.9402	0.9914
60 75	84	1	71	0.9570	0.8805	0.9849
75 90	12	0	12	0.9570	0.8805	0.9849

The failure function (cumulative incidence of mortality) in the entire cohort by the Kaplan-Meier method and by the competing risk method are shown in Table 6 (**complete data in additional file 4**). Our data suggests that there was approximately 5.5% chance of dying by COVID-19 in the first 71 days after OTS.

Table 6
Failure of function entire cohort.

Failure function. Entire cohort											
Kaplan -Meier method						Competing Risk method					
Time	Beg.	Deaths	Net Lost	Failure function	[95% Conf. Int.]		EndStatMort	Time	R (IA1c)	(95% Conf. Interval)	
2	184	1	0	0.0054	0.0008	0.0379	Dead by COVID	2	0.0054	0.0005	0.0277
19	183	1	1	0.0109	0.0027	0.0428	Dead by COVID	19	0.0109	0.0022	0.0357
28	181	0	1	0.0109	0.0027	0.0428	Dead (othercause)	28	0.0109	0.0022	0.0357
31	179	1	0	0.0164	0.0053	0.0500	Dead by COVID	31	0.0163	0.0045	0.0436
41	174	1	1	0.0220	0.0083	0.0577	Dead by COVID	41	0.0219	0.0073	0.0516
71	29	1	11	0.0558	0.0162	0.1828	Dead by COVID	71	0.0553	0.0121	0.1496
76	10	0	10	0.0558	0.0162	0.1828	Alive	76	0.0553	0.0121	0.1496

The Kaplan-Meier failure function by surgery group showed that the risk of mortality at 76 days or before was 0.1563 (Table 7) (**complete data in additional file 4**). The comparison of K-M and life tables of survival (actuarial method) curves by GS are shown in Figs. 1 and 2. The differences in survivor curves by GS were statistically significant and established that GS 4 presented a lower survival function compared to the rest of the surgery groups (**complete data in additional file 5**).

Table 7
Failure of function by Group of Surgery.

Failure function by Group of Surgery						
Kaplan-Meier method						
Time	Beg.	Fail	Lost	Failure function	(95% Conf. Interval)	
Group 1						
76	4	0	4	0.00	.	
Group 2						
76	2	0	2	0.00	.	
Group 3						
76	1	0	1	0.00	.	
Group 4						
2	65	1	0	0.0154	0.0022	0.1042
19	64	1	0	0.0308	0.0078	0.1175
28	63	0	1	0.0308	0.0078	0.1175
31	62	1	0	0.0464	0.0152	0.1370
41	59	1	0	0.0626	0.0239	0.1582
71	10	1	3	0.1563	0.0465	0.4545
76	4	0	4	0.1563	0.0465	0.4545

Looking at the pathology and type of treatment performed in the COVID-19 death patients, 1/5 died after a shoulder fracture treated by arthroplasty and 4/5 after hip fractures.

The final selected models adjusted by confounders and analyzed by a Cox Regression model (effect based on HR) and by Fine-Gray Regression model demonstrated that the "Age" adjusted for "HBP" showed the highest association with mortality by COVID-19 (Hr: 1.145; SHR: 1.144), while the model "Age" adjusted for: "Group of Surg", "HBP", "RespHist presented a lower association but significant too. (HR and SHR: 1.111) Table 8. The diagnosis of the models demonstrated that the proportional hazard assumption was accepted based on Schonefeld residuals ($P=0.405$) and on the test of interaction between survival time and the independent variables ($P=0.857$). The log lineal assumption was also accepted ($P=0.406$) (complete data in additional file 7).

Table 8
Final selected models adjusted by confounders

Model	Cox Regression				Fine-Gray Regression			
	HR	p value	(95% Conf. Interval)		SHR	p value	(95% Conf. Interval)	
Age Adjusted for: "Group of Surg", "HBP", "RespHist"	1.111	0.039	1.005	1.228	1.111	0	1.049	1.176
Age Adjusted for: " Group of Surg ", "RespHist"	1.111	0.039	1.005	1.228	1.109	0.001	1.046	1.177
Age Adjusted for: "Group of Surg"	1.112	0.042	1.004	1.232	1.11	0.001	1.046	1.179
Age Adjusted for: "HBP"	1.145	0.005	1.042	1.257	1.143	0	1.088	1.201
Age Adjusted for: "RespHist"	1.145	0.003	1.046	1.254	1.144	0	1.088	1.202

Discussion

The results of this study demonstrated that the risk and IR of COVID-19 in patients who underwent OTS were similar for the different GS; however, the cumulative survival probability in patients who had bone and arthroplasty procedures in big joints (GS 4) was significantly inferior, with 15.63% chance of dying by COVID-19 at 76 days post-surgery or before. The age adjusted by GS, HBP and history of respiratory disease was associated to the mortality. At the end of the follow-up, there was a 94.42% chance of surviving 76 days or more after OTS.

The risk of COVID-19 diagnosis (considering all types of diagnose) was 14.13% (95% CI: 9.83–19.90%) for the entire cohort. On May 5, 2020, in Madrid with a total population of 6,663,394 (23), there were 62,989 confirmed cases (0.95%); 40,851 had been admitted (64.86% of all cases, and 0.61% of the entire population) and 8,420 had died (13.37% of all cases, and 0.13% of the entire population)(24). A seroprevalence study, performed at that time in Spain, showed an 11.3% (95% CI: 9.8 to 13.0) rate of infection and a percentage of suspected cases of 19.7%. Considering all these data, the risk of diagnosis, including suspected cases, in our cohort is similar to the general population.

The relative risk of all COVID-19 diagnoses by the different GS was not statistically significant, when compared with group 1 as the reference; thus, the grade of aggression and inflammation cannot be considered as a factor of a higher risk of infection in our cohort.

Notably, the most interesting variable to analyze is the probability of survival. In our study the chance of survival at 76 days or more in a patient who had OTS was 94.42% (81.72–98.38). This high survival probability gives hope compared with results obtained in previous studies. Lei et al.(4), reported a mortality rate of 20.5% after elective surgery; the COVIDSurg Collaborative group showed a crude 30-day mortality rate of 23.8% in the entire cohort and of 28.8% in the orthopedic surgery cohort. In those studies, all patients developed the disease before five days after surgery, or the COVID-19 infection was confirmed preoperatively thus, they were already infected. This may be the most important difference: the patients in our study were healthy (not infected). The mortality probability after having an OTS, even in an uncontrolled transmission area, is low if the patient has not been infected previously.

Regarding the influence of the aggression and inflammation of the OTS on mortality, there were no deaths in groups 1, 2 and 3. All deaths were concentrated in group 4 and the lower survival function was statistically significant in this group. Lei et al(4), have concluded that a more complex surgery increases the risk of worst evolution; however, they detect several variables (older age and comorbidities) that are more frequent in this group, although there was no multivariate model adjusted for the confounders.

The influence on higher mortality rate in older patients has been reported in few studies with a high number of patients(25) (26). Their data are similar to our model of explanation, in which age was the most important variable. The age adjustment for the GS, HBP, and respiratory history, were some of the best models for explaining the association of mortality by COVID-19 in patients who underwent OTS with a confirmed proportional hazard and log lineal assumptions requiring the model diagnosis.

This study has some limitations. We could not define a nonsurgical subgroup in our cohort during the same recruitment period. In our study, not all types of OTS, such as spine surgery or pediatric surgery, were included (because they are performed in another hospital). Representative of the general OTS population and changes in case definitions should be considered when making inferences from the risks and incidence rates of infection by COVID-19 observed in our cohort(27). To the best of our knowledge, the highlight of this observational study is that this is a cohort with a high number of OTS patients (without a COVID-19 infection) operated in a “non-controlled spread COVID-19 scenario”; thus, these data could help clarify the risk of infection and survival probability and aid in decision-making between waves in which the community transmission rate could increase again.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethics Commission of the Infanta Leonor University Hospital and Virgen de la Torre Hospital. Reference number 026-20

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Most of the materials can be found in the additional material

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

DC and MC have made the acquisition of data.

FC and RR have done the design of the work, analysis, interpretation of data and drafted the work

RL has substantively revised the work.

All authors read and approved the final manuscript

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Figures

Figure 1

Kaplan-Meier survival by Group of Surgery.

Figure 2

Proportion Surviving by Group of Surgery.

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