Induction immunosuppression and outcome in kidney transplant recipients with early COVID-19 after transplantation

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ABSTRACT

COVID-19 in kidney transplants has a high risk of complications and mortality, especially in older recipients diagnosed during the early period after transplantation. Management of immunosuppression has been challenging during the pandemic. We investigated the impact of induction immunosuppression, either basiliximab or thymoglobulin, on the clinical evolution of kidney transplants developing COVID-19 during the early period after transplantation. Kidney transplant recipients with less than 6 months with a functioning graft diagnosed of COVID-19 from the initial pandemic outbreak (March 2020) until July 31st, 2021 from different Spanish centers participating in a nationwide registry. A total of 127 patients from 17 Spanish centers developed COVID-19 during the first 6 months after transplantation, 73 (57.5%) received basiliximab and 54 (42.5%) thymoglobulin. Demographics were not different between groups but patients receiving thymoglobulin were more sensitized (cPRA of 32.7±40.8% vs. 5.6±18.5%) and were more frequently re-transplants (30% vs. 4%). Recipients older than 65 years treated with thymoglobulin showed the highest rate of acute respiratory distress syndrome (64.7% vs. 37.1% for older recipients receiving thymoglobulin and basiliximab [$p<0.05$], and 23.7% and 18.9% for young recipients receiving basiliximab and thymoglobulin [$p>0.05$]) and the poorest survival (mortality rate of 64.7% and 42.9% for older recipients treated with thymoglobulin and basiliximab, respectively [$p<0.05$], and 8.1% and 10.5% for young recipients treated with thymoglobulin and basiliximab [$p>0.05$]). Older recipients treated with thymoglobulin showed the poorest survival in the Cox's regression model adjusted for comorbidities. Thus, thymoglobulin should be used with caution in older recipients during the present pandemic era.

Keywords: basiliximab, COVID-19 infection, lymphocyte-depleting agents, renal transplantation

INTRODUCTION

Coronavirus disease 2019 (COVD-19) emerged as a pandemic in December 2019. Infection has spread quickly and renal transplant recipients receiving chronic immunosuppression have been considered a population at high risk of infection, complications and death. In these last months a large amount of information from nationwide registries, multicentre and single-centre studies have been reported. Major complications such as acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS) were very frequent in renal transplant patients with a high comorbidity burden (1). Importantly, kidney transplant recipients have experienced a high mortality rate, especially among older recipients (>65 years) who acquired the infection during the early post-transplant period (< 6 months) (2).

In this pandemic era, management of induction and maintenance immunosuppression has been challenging to clinicians treating kidney transplant recipients. Regarding the use of induction therapy with lymphocyte-depleting agents (anti-thymocyte globulins, alemtuzumab and rituximab), a large study conducted in the USA showed that their use decreased during the first weeks after the outbreak as compared with the three previous years, while the use of basiliximab or no induction increased (3). Importantly, while lymphocyte-depleting agents have been associated with a lower risk of acute rejection, no differences in mortality rates have been reported (3). Additionally, other small, single centre studies have reported that renal transplant patients treated with thymoglobulin who acquired COVID-19 early after transplantation display a modest risk for severe disease, especially using low doses (4). Thus, it is necessary to investigate the potential different impact of the type of induction therapy on patient and graft outcomes in larger cohorts of kidney transplant recipients who acquired COVID-19 during the initial months after transplantation.

Since the beginning of the pandemic, renal transplant units from Spain were requested to report all cases diagnosed of COVID-19 to the Spanish Transplant National Organization (ONT). This registry has contributed to characterize the epidemiology and risks factors in the solid organ transplant

Spanish population (2)(5)(6). For the present study, detailed information on renal transplants recipients diagnosed of COVID-19 during the early period after transplantation (less than 6 months) was recorded. The aim is to characterize the influence of anti-lymphocyte depleting agents (thymoglobulin) in the clinical course of infection in comparison to patients treated with interleukin-2 receptor antibodies (basiliximab).

MATERIALS AND METHODS

Patients

The data collection included recent kidney transplant recipients (less than 6 months) who had been diagnosed of COVID-19 from the start of the pandemic in Spain until July 31, 2021. Centers throughout the Spanish territory were requested to provide information on each case of COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR) in a sample of the respiratory tract. The study was approved by the National Transplant Commission of the Interregional Council of the National Health System.

Variables

Data from donors (donor type, age and sex), recipients (age, sex, comorbidities such as hypertension, diabetes mellitus, obesity defined as body mass index >30 Kg/m^2, history of previous cancer, previous lung disease) and transplant related variables (date of transplantation, number of previous transplants, HLA ABDR mismatches, induction treatment: ATG or Basiliximab, maintenance treatment: tacrolimus associated to mycophenolate and prednisone, tacrolimus associated to mTOR inhibitors (mTOR-i) and prednisone or other combinations, delayed graft function and acute rejection) were recorded. Vaccination status with an mRNA vaccine, date of diagnosis of SARS CoV2 infection, hospitalization, nosocomial infection, acute respiratory distress syndrome (ARDS), admission to the intensive care unit (ICU), mechanical ventilation, acute kidney injury (AKI), dialysis requirements (HD), graft failure and patient death were also recorded. In addition, different laboratory variables (serum creatinine, total lymphocyte count, D dimer, interleukin-6 and C reactive

protein) at the time of diagnosis (day 0), 7, 14, 21 days and at the end of follow-up were recorded.

Statistical analysis

Qualitative variables are described as absolute numbers and percentages and quantitative variables are presented as the mean and standard deviation or as the median and interquartile range (IQR), depending on the sample distribution. Categorical variables were compared by the Chi-squared test and quantitative variables by the unpaired t-test or the non-parametric Mann-Whitney U test.

Kaplan-Meier survival curves were used to analyze patient survival with the log-rank test for comparisons. Univariate and multivariate Cox regression analysis was employed to analyze patient survival.

Linear mixed models for repeated measures were employed to analyze the evolution of the different lab values in patients treated with thymoglobulin and basiliximab.

Statistical analyses were performed using Stata software version 16 (Stata Corp, College Station, TX, USA).

RESULTS

Baseline patient characteristics

Seventeen out of the 40 renal transplants units from Spain participated in the study and 127 patients with an early (less than 6 months) COVID -19 infection after transplantation were recorded. From this set of patients, 73 (57.5%) received induction treatment with basiliximab and 54 (42.5%) were treated with thymoglobulin. In table 1, clinical characteristics from donors and recipients as well as transplant-related variables according to induction therapy are shown. Demographic data from donors and recipients were not significantly different between groups. Comorbidities among recipients were also not different between groups, except that diabetic recipients were more frequently treated with basiliximab (69% vs. 51%; p-value 0.045). As expected, patients receiving induction with thymoglobulin have a higher cPRA at the time of transplant (32.7±40.8% vs. 5.6±18.5%; p-value < 0.001) and were more

frequently recipients of a re-transplant (30% vs. 4%; p-value < 0.001). The rate of DGF was not different between groups (38% for basiliximab treated patients vs. 32% for thymoglobulin treated patients) and the low rejection rate was also not different between groups (4.1% for basiliximab vs. 7.4% for thymoglobulin).

Only 19 transplants recipients from this cohort received at least one dose of an mRNA SARS-CoV-2 vaccine (12 receiving basiliximab and 9 receiving thymoglobulin) and only 12 patients have completed a fully vaccination 15 days before transplantation precluding further analysis of this variable.

Evolution after COVID-19 diagnosis

COVID-19 was diagnosed at 3.0±3.0 months in basiliximab treated patients and at 2.2±2.0 months in the thymoglobulin group (p=0.888). The rate of hospitalization (86% and 83%) as well as the rate of nosocomial acquired infection (45% vs. 43%) were high and not different between groups. Similarly, the rate of ARDS (30% vs. 33%), intensive care unit admission (24.7% vs. 20.4%) and respiratory failure requiring mechanical ventilation (17.8% vs. 16.7%) were not different between groups. AKI rate was high in both groups (43.4% vs. 40.7%) and dialysis supportive treatment was also frequently required (20.5% vs. 24.1%).

Patient survival

Mortality rate in the overall set of patients was 26% (33 out of 127 patients) and was not different between patients receiving basiliximab or thymoglobulin. Kaplan-Meier analysis showed that patient´s age was closely associated with patient's survival (figure 1) while induction therapy was not (figure 2). Since old recipients tended to receive less frequently thymoglobulin (p=0.086), we analyzed outcome in young and older recipients categorized according to induction therapy. Transplant recipients younger than 65 years either treated with basiliximab or thymoglobulin exhibited a similar survival. However, recipients older than 65 years had a poorer survival in thymoglobulin treated than in basiliximab treated transplants (figure 3). Noticeably, while 15 out of 35 patients older than 65 years (42.9%) treated with basiliximab died, up to 11/17 (64.7%) patients older than 65 years treated with thymoglobulin died (p<0.05). In the case of young recipients, these data were 4 out of 38 patients

(10.5%) treated with basiliximab and 3 out of 37 (8.1%) patients treated with thymoglobulin. Similar data were observed if the analysis was done in recipients acquiring the infection during the first 3 months after transplantation (death rates of 22% for young recipients treated with basiliximab, 10% for young recipients treated with thymoglobulin, 41% for older recipients treated with basiliximab and 78% for older recipients treated with thymoglobulin; p=0.005). Among recipients who acquired the infection from the 3rd to 6th month (n=39), mortality rate was 0% in recipients younger than 65 years either treated with basiliximab or thymoglobulin, but it was significantly higher (p=0.0008) in patients older than 65 years without statistically significant differences between thymoglobulin and basiliximab treated patients (62% and 43%, respectively).

ARDS was also more frequently observed in older recipients receiving thymoglobulin than in the other groups (64.7% vs. 37.1% for older recipients receiving thymoglobulin and basiliximab, respectively [p<0.05], and 23.7% for young recipients receiving basiliximab and 18.9% for young recipients receiving thymoglobulin [p=NS]).

Risks factors for patient's death are summarized in table 3. As previously described, comorbidities of the recipient (diabetes and obesity) were associated with survival. Maintenance immunosuppression with tacrolimus and mycophenolate tended to be associated with a poorer survival than maintenance with tacrolimus and mTOR inhibitors, but the low number of patients treated with tacrolimus and mTOR inhibitors (n=15) precluded further analysis. Multivariate Cox's regression analysis showed that older recipients treated with thymoglobulin had the poorest survival adjusting for baseline comorbidities (table 3). Furthermore, DGF did also independently correlate with patient death.

Laboratory data

Patients treated with thymoglobulin showed a lower number of circulating lymphocytes at the time of diagnosis (table 1). Linear mixed models for repeated measures showed than lymphopenia tended to recover in both groups of patients as the infection evolved but the recovery was slower in patients treated with thymoglobulin than in patients treated with basiliximab (figure 4).

Acute phase reactants and D dimer were not different between groups at baseline (table 1) and during the first month (data not shown). As expected, baseline acute phase reactants (interleukin-6 and C reactive protein) and D dimer levels were closely associated with survival.

DISCUSSION

In the present study we analyzed a cohort of renal transplant recipients with COVID-19 diagnosis early after transplantation (less than 6 months). As it has been previously reported, we confirmed that recipients older than 65 years with a higher comorbidity burden showed a higher mortality than younger patients. Remarkably, among older recipients, thymoglobulin induction therapy was an independent factor predicting higher risk of ARDS and death. As expected, lymphopenia was significantly more profound in patients treated with thymoglobulin than in those treated with basiliximab.

In Spain, the standard of care for renal transplant recipients receiving a kidney from a brain death or living donor is based on induction therapy with basiliximab whereas thymoglobulin is restricted to high immunological risk transplants. However, management of induction immunosuppression in the case of donors after controlled circulatory death is rather heterogeneous (7). The standard of care for maintenance immunosuppression is tacrolimus, mycophenolate and steroids but some centers have moved to a maintenance regimen based on tacrolimus and mTOR inhibitors (8). Our set of patients, containing one third of transplants from donors after circulatory death, reflects these heterogenous policies and includes a significant number of patients treated with both induction regimens. In this study cohort, the nosocomial acquired infection was highly prevalent (44%), especially during the first and second waves, indicating that infection was acquired during the first admission or after re-admission due to transplant-related complications.

Since the beginning of the pandemics, patient age and comorbidities associated with aging have been repeatedly associated with outcomes after COVID-19 in both, the general population (9) and in renal transplant recipients (10). Different case-control studies with propensity score matching tried to

elucidate whether chronic immunosuppression received by solid organ transplant recipients is a risk factor for COVID-19 complications and death. A number of studies concluded that the increased risk in solid organ transplant recipients is related to the high burden of comorbidities (11)(12)(13)(14)(15) despite others observed a higher COVID-19-related mortality compared to a matched nontransplant hospitalized cohort (16). However, in these large nationwide or multicenter studies, the proportion of patients who acquire the infection during the initial months after transplantation was low and was not specifically analyzed. It is well-known that the strong immunosuppression employed during the first months after transplantation is associated with a highest risk of viral infections and severity during this early period. Initial reports with low number of patients (17), and confirmed later in larger studies, have shown that the fatality rate related to COVID-19 is higher among elderly recipients acquiring the infection during the early period after transplantation approaching to the 50% of cases (2). Our set of patients containing patients included in the previous studies confirm these data in a larger sample size.

The transplant community agrees that during the current COVID-19 pandemic, the benefit-harm of immunosuppression should be well-balanced. Among immunosuppressants, administration of lymphocyte-depleting agents during the peri-transplant period might increase the risk of COVID-19 related complications. In our study, recipients younger than 65 years have a similar clinical evolution in patients treated either with basiliximab or thymoglobulin, suggesting that these patients may safely receive both induction therapies without increasing the risk of major complications in case of early COVID-19 infection. Conversely, recipients older than 65 years receiving thymoglobulin show a significantly higher risk of ARDS and COVID-19 related mortality than patients treated with basiliximab. Among the increasing older populations receiving a renal transplant (18) (19), it has been described that immune senescence and frailty increase the risk for infections during the first months when transplant recipients are receiving a higher degree of immunosuppression. (20). Thus, combined with age-related immune senescence, delivery of immunosuppressive therapy remains a challenging issue given the delicate balance between rejection and infections in older

recipients. Despite current transplantation guidelines provide no specific recommendations for induction or maintenance immunosuppression for older recipients, anti-thymocyte globulin induction immunosuppressive therapy in older recipients has been associated with an increased risk of infectious complications (21). In this regard, Bae et al, using data from the Scientific Registry of Transplant Recipients studied kidney-only transplant recipients during the pre-pandemic era (from January 1, 2017, to March 12, 2020; n = 5035) and the pandemic era (from March 13, 2020, to July 31, 2020; n = 5035) and compared the use of lymphocyte-depleting agents versus basiliximab or no induction. Interestingly, the use of lymphocyte-depleting agents was associated with decreased risk of rejection but with no significant difference in mortality during the pandemic era. However, mortality risk among the infected elderly population was not analyzed. Similarly, a single center concluded that thymoglobulin use either as induction protocol or as anti-rejection treatment during the COVID-19 pandemic appears to be safe, although the number of patients with COVID-19 was very low (only 2 cases) and a limited number of patients older than 65 years were included (22). In our study, the number of patients older than 65 years receiving thymoglobulin was relatively low (n=17) but the fatality rate was very high (64.7%), suggesting that this treatment should be employed with caution in this population.

It is very important to note that most patients included in the present study were transplanted before the SARS-CoV-2 vaccines were available. Thus, these outcomes may not fully reflect the current clinical situation where most transplant candidates have been actively immunized before transplantation (23).

In summary, in this retrospective, nationwide Spanish registry cohort study we show that renal transplant recipients older than 65 years developing COVID-19 during the early post-transplant period have a high mortality, especially if they received thymoglobulin as induction therapy. Thus, these data suggest that thymoglobulin induction among elderly transplant recipients should be well-balanced and used with caution during the present pandemic era, especially among patients not previously vaccinated against SARS-CoV-2.

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CONFLICT OF INTEREST STATEMENT

None to be declared.

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Table 1. **Clinical characteristics and lab tests at the time of COVID-19 diagnosis according to the induction treatment**

Variables	Basiliximab (n= 73)	Thymoglobulin (n= 54)	*p-value*
Donor type (DBD / cDCD / LD)	44/22/7	29/21/4	0.575
Donor age. years	60.7 (14.9)	59.7 (12.9)	0.339
Donor sex. m/f	37/35	34/18	0.120
Patient age. years	59.4 (18.0)	58.2 (12.7)	0.337
Patient age > 65 years. y/n	34/39	17/37	0.086
Patient sex. m/f	46/27	31/23	0.523
Arterial Hypertension. y/n	64/9	46/8	0.684
Diabetes. y/n	33/40	15/39	**0.045**
BMI > 30 Kg/m^2. y/n	17/56	12/41	0.932
Previous cancer. y/n	12/61	10/44	0.759
Pneumopathy. y/n	11/62	9/45	0.807
Re-transplant. y/n	3/70	16/38	**0.000**
cPRA (%)	5.6 (18.5)	32.7 (40.8)	**0.000**
HLA mm	3.7 (2.2)	4.2 (2.4)	0.198
Maintenance immunosuppression (TAC+MMF+P / TAC+mTOR-i+P)	62/11	50/4	0.186
DGF. y/n	28/45	17/37	0.423
Acute rejection. y/n	3/68	4/49	0.428
Transplant to COVID-19 time. months	2.5 (2.7)	3.2 (3.4)	0.888
Hospitalization. y/n	63/10	44/10	0.461
Nosocomial infection. y/n	33/40	23/30	0.840
ARDS. y/n	22/51	18/36	0.701
ICU admission. y/n	18/55	11/43	0.569
Invasive mechanical ventilation. y/n	13/60	9/45	0.867
Acute kidney injury. y/n	32/36	22/30	0.604
Hemodialysis requirement. y/n	15/56	13/41	0.654
Death. y/n	54/19	40/14	0.990
Survival time. months	7.8 (6.3)	7.2 (5.8)	0.289
Laboratory data at the time of diagnosis			
Creatinine. mg/dL	2.7 (2.1)	2.4 (1.8)	0.465
Total lymphocytes. x10^9/L	556 (389)	426 (361)	**0.016**

D-dimer. ng/mL	2961 (5459)	1591 (1405)	0.327
Interleukin-6. pg/mL	113 (296)	105 (134)	0.385
C-reactive protein. mg/dL	26.1 (42.5)	21.6 (35.4)	0.830

Qualitative variables are presented as raw numbers (n). Continuous variables are expressed as the mean (and standard deviation. SD). Comparison between groups was performed using Pearson' χ^2 test for categorical data. T-tests were used for normally continuous distributed data and Mann-Whitney U test for non-normally distributed data.

DBD: donation after brain death. cDCD: controlled donation after circulatory death; LD: living donation; BMI: body mass index; cPRA: calculated panel reactive antibody; HLA mm: human leukocyte antigen antibodies mismatch at A-B-DR loci; ATG: anti-thymocyte globulin; TAC: tacrolimus; MMF: mycophenolate; P: prednisone; mTOR-i: mammalian target of rapamycin inhibitors; DGF: delayed graft function; COVID-19: coronavirus disease; ARDS: acute respiratory distress syndrome; ICU: intensive care unit.

Table 2. Clinical characteristics and lab tests at the time of COVID-19 diagnosis and survival

Variables	Recovered (n= 94)	Non-Survivors (n= 33)	*p-value*
Donor type (DBD / cDCD / LD)	54/29/11	19/14/0	0.089
Donor age. years	57.5 (14.6)	68.0 (8.6)	**0.000**
Donor sex. m/f	51/41	20/12	0.487
Patient age. years	56.1 (13.9)	66.7 (18.7)	**0.000**
Patient age > 65 years. y/n	26/68	25/8	**0.000**
Patient sex. m/f	56/38	21/12	0.681
Arterial Hypertension. y/n	79/15	31/2	0.151
Diabetes. y/n	28/66	20/13	**0.002**
BMI > 30 Kg/m^2. y/n	15/78	14/19	**0.002**
Previous cancer. y/n	13/81	9/24	0.079
Pneumopathy. y/n	13/81	7/26	0.317
Re-transplant. y/n	11/83	8/25	0.082
cPRA. %	14.7 (31.0)	24.2 (36.3)	0.076
HLA mm	4.0 (2.5)	3.6 (1.8)	0.845
Induction therapy (Basiliximab/ATG)	54/40	19/14	0.990
Maintenance immunosuppression (TAC+MMF+P / TAC+mTOR-i+P)	80/14	32/1	0.069
DGF. y/n	26/68	19/14	**0.002**
Acute rejection (y/n)	7/87	34/0	0.188
Transplant to COVID-19 diagnosis time (month)	3.0 (3.3)	2.2 (2.0)	0.915
Hospitalization. y/n	74/20	33/0	**0.004**
Nosocomial infection. y/n	37/56	19/14	0.077
ARDS. y/n	11/83	29/4	**0.000**
ICU admission. y/n	14/80	15/18	**0.000**
Invasive mechanical ventilation. y/n	8/86	14/19	**0.000**
Acute kidney injury. y/n	33/56	21/10	**0.003**
Hemodialysis requirement. y/n	10/81	18/15	**0.000**
Lab tests at diagnosis of COVID-19			
Creatinine. mg/dL	2.1 (1.5)	3.6 (2.4)	**0.011**
Lymphocytes. x10^9/L	510 (386)	479 (377)	0.653
D-dimer. ng/mL	1581 (1627)	4247 (7169)	**0.007**
Interleukin-6. pg/mL	49 (62)	227 (390)	**0.002**
C-reactive protein. mg/dL	17 (30)	41 (53)	**0.002**

Qualitative variables are presented as raw numbers (n) or frequencies. Continuous variables are expressed as mean and standard deviation (SD). Comparison between groups was performed using Pearson' χ^2 test for categorical data. T-tests were used for normally continuous distributed data.

DBD: donation after brain death. cDCD: controlled donation after circulatory death; LD: living donation; BMI: body mass index; cPRA: calculated panel reactive antibody; HLA mm: donor

recipient human leukocyte antigen mismatches at the A-B-DR loci; ATG: anti-thymocyte globulin; TAC: Tacrolimus; MMF: Mycophenolate; P: prednisone; mTOR-i: mammalian target of rapamycin inhibitors; DGF: delayed graft function; COVID-19: coronavirus disease; ARSD: acute respiratory distress syndrome; ICU: intensive care unit.

Table 3. Risk factors associated with mortality in kidney transplant recipients with COVID-19 diagnosis during the initial 6 months after transplantation

Variable	Univariate analysis Hazard rate (95% CI)	*p-value*	Multivariate analysis Hazard rate (95% CI)	*p-value*
Patient age > 65 years	0.985 (0.939 – 1.034)	0.007		
Thymoglobulin induction	1.955 (0.880 – 4.342)	0.100		
Patient age and induction				
Age > 65 & Thymoglobulin	1 (reference)		1 (reference)	
Age > 65 & Basiliximab	0.397 (0.174-0.905)	0.028	0.425 (0.187-0.967)	0.041
Age < 65 & Thymoglobulin	0.049 (0.011-0.225)	0.000	0.095 (0.026-0.349)	0.000
Age < 65 & Basiliximab	0.111 (0.035-0.357)	0.000	0.104 (0.032-0.340)	0.000
Diabetes	2.809 (0.908-4.579)	0.038	1.821 (0.541-2.584)	0.674
BMI > 30 Kg/m^2	3.021 (1.511-6.024)	0.002	2.439 (1.168-5.050)	0.016
Previous cancer	2.049 (0.951-4.225)	0.067		
Re-transplant	1.989 (0.897-4.412)	0.091		
cPRA (%)	1.007 (0.988-1.016)	0.136		
TAC+MMF+P	4.871 (0.665-35.69)	0.119		
DGF	2.915 (1.460-5.848)	0.002	2.825 (1.383-5.780)	0.004

BMI: body mass index; cPRA: calculated panel reactive antibodies; TAC: Tacrolimus; MMF: Mycophenolate; P: prednisone; DGF: delayed graft function

Figure 1

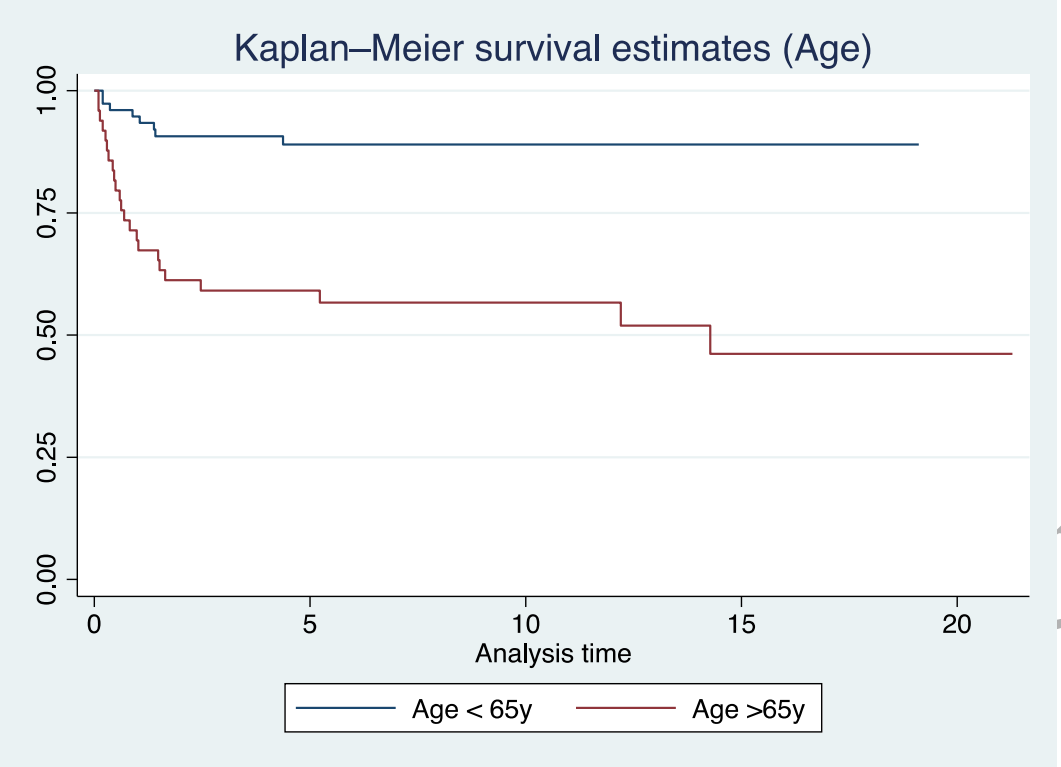

Figure 2

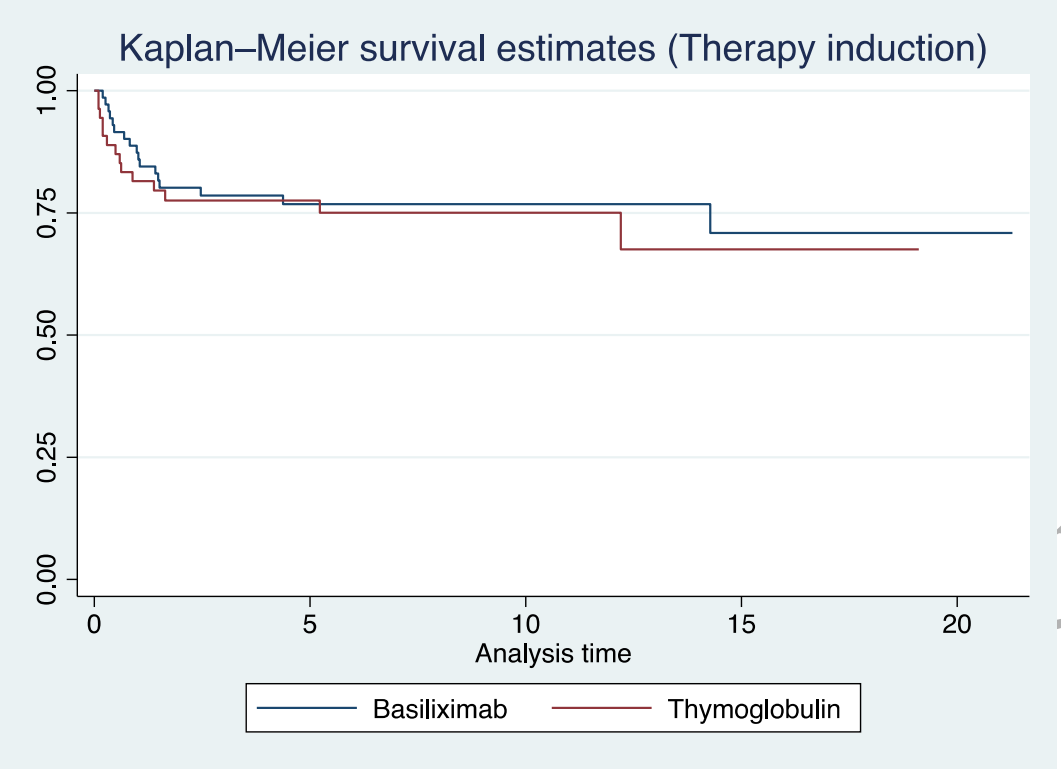

Figure 3

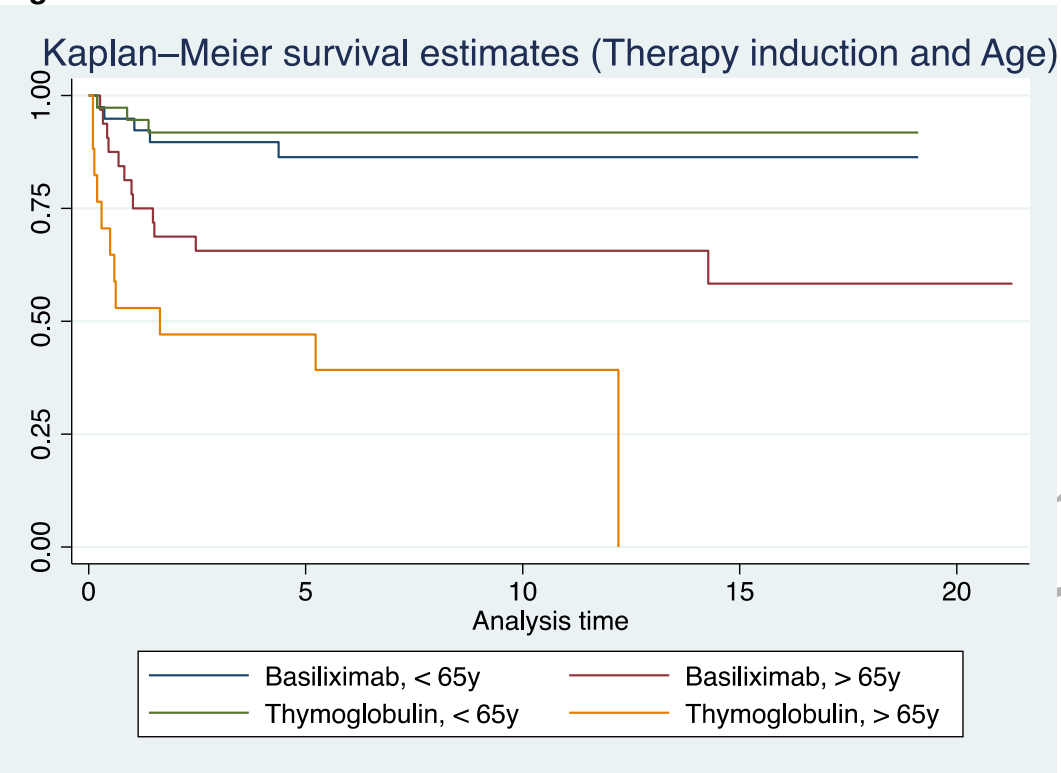

Figure 4