Frailty-independent Undertreatment Negative Impact on Survival in Older Patients With Breast Cancer

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ABSTRACT

Introduction: The management of older patients with breast cancer remains controversial. The difficult assessment of ageing idiosyncrasies and the insufficient evidence of therapeutic guidelines can lead to undertreatment. Our goal was to measure undertreatment and assess its impact on survival.

Materials and methods: Consecutive patients with breast cancer aged 70 years or older were prospectively enrolled in 2014. Three frailty screening tools (G8, fTRST, GFI) and two functional status scales (KPS, ECOG-PS) were applied. Disease characteristics, treatment options and causes of mortality were recorded in a 5-year follow-up. We defined undertreatment and correlated its survival impact with frailty.

Results: A total of 92 patients were included. Median age was 77 (range 70-94) years. The prevalence of frailty was discordant (G8: 41,9%, fTRST: 74.2%, GFI: 32.3%). A low-risk disease was not found (51.2% were N+) probably due to a late diagnosis (76.1% based on self-examination). Thirty-three patients (35.6%) died 15 of them from breast cancer. We found a considerable high proportion (53.3%) of undertreatment, which had a frailty-independent negative impact on 5-year survival (HR=5.1 [95% CI: 2.1-12.5]). Additionally, omission of surgery had a frailty-independent negative impact on overall survival (HR=3.9 [95% CI: 1.9-7.9]).

Conclusion: Breast cancer treatment in older adults ought to be individualized. More important than assessing frailty (not to treat) is essential to be aware of the risk-benefit profile and the patient's well-informed willingness to be treated. The undertreatment in daily practice is frequent and might have, as we report, a negative impact on survival.

Keywords: Breast cancer, older adult, geriatric assessment, undertreatment, survival

Highlights:

The breast cancer treatment in older adults must be individualized

The prevalence of frailty on screening scales is discordant

Half of older adults with breast cancer are undertreated in daily practice

The undertreatment in older patients with breast cancer has a significant negative impact on 5-year survival

The omission of surgery in older patients with breast cancer has a negative impact on 5-year survival

INTRODUCTION

Population extended lifespan is an emerging reality [1,3]. In Portugal, in the last sixty years, the population aged 65 or over almost tripled from 8% in 1961 to 22% in 2019 [2]. In 2050, the over-65 population in the European Union (EU) will reach 28.5%, with women outnumbering men. [3].

The increased longevity of older adults has led to a growing incidence of cancer, a disease associated with ageing. A higher proportion of women will warrant the foreseen rising incidence of breast cancer (BC) reaching a peak in women aged 70-84 years [4-6]. BC is the commonest cancer affecting European women with significant survival improvement in the last decades. The 5-year relative survival is 82% in the EU, 83% in Portugal, and 90% in the USA but with pronounced differences between age groups and significantly worst in older patients (50% in over-75 women) [4-6]. Despite competing non-cancer mortality causes, BC is the cause of death in up to 40% of over-80 women [7].

The best multimodality therapeutic strategy in older patients with BC has always been and will remain controversial [7,10-13]. Chronological age alone should not condition it [7,11,38]. The decision-making at the multidisciplinary meeting (MDM) should be standardized and supported by level 1 evidence and simultaneously individualized after a multidimensional evaluation. Therefore, it is crucial to standardize the widely recommended geriatric assessment strategy in oncology [7,8,11]. Too many and distinct tools described in the literature to assess the functional, nutritional, cognitive status, comorbidities, polymedication, and geriatric syndromes hamper a consensus about the MDM's best daily practice solution for a tailored plan [9,29-34]. Moreover, the well-known underrepresentation of older adults in randomized controlled trials (RCT) evaluating cancer treatments due to the heterogeneity of their vulnerable physiology, confounding comorbidities or drug interactions, and the likely lower adherence to therapy or the competing non-cancer mortality hinder to obtain evidence-based guidelines [13-16]. Women older than 70 were precluded even from the paradigm-changing Veronesi's Milan trials that validated breast conservative surgery (BCS) [17].

In older women, the myth of BC being biologically less aggressive, the stigma of chronological age and the unknown benefit of several treatments (standard for younger patients) are the main reasons for frequent undertreatment that might affect cancer lethality [11,13,15]. Defining undertreatment in the older patients, especially in the frailty ones, is not consensual. It is often considered when internationally defined therapeutic standards are not followed. Knowing when and how to treat, considering

compliance to the proposed treatment, its potential adverse effects, avoiding undertreatment with impact on survival, and knowing individual patient preferences and precluding unnecessary overtreatment, requires a well-trained clinical communication with the older patient and her caregiver and family [18,30].

This study aimed to evaluate undertreatment and its potential impact on 5-year survival in an older adult population aged 70 or over, with BC treated in 2014 at the Breast Center of São João University Hospital (CM-CHUSJ).

MATERIALS AND METHODS:

Our study enrolled 92 consecutive patients over-70 years with *de novo* BC from January to December 2014. Data were obtained prospectively during routine medical visits and retrieved from patient's digital records. Patients admitted with locoregional or distant recurrences of a previous BC were excluded. The 5-year follow-up ended on December 31st, 2019.

Sociodemographic characterization and an evaluation of the activities of daily living (ADLs), using the Lawton-Brody scale (scores 0: dependent and 1: autonomous) were registered [19]. We also assessed the psychological context, using the Hospital Anxiety-Depression Scale, focusing our measurement on its depressive component (scores 0-7: healthy, 8-11: borderline and ≥12: psychopathology) [20]. The questionnaires were carried out in person or by telephone. The source of information was the patient in 80% or a family member in 20%. The application time had an average of 7 (range 5-12) minutes.

A geriatric assessment was made in an additional hospital visit before the MDM, by applying three frailty screening tools – Geriatric 8 (G8)(score ≤14: frailty, ≥15: risk absent)[21], Flemish version of the Triage Risk Screening Tool (fTRST)(frailty if ≥ 1 point, risk absent if 0 points)[22] and the Groningen Frailty Indicator (GFI)(4-15 points: frailty, 0-3 points: risk absent)[23], combined with two functional assessment scales, the Karnofsky performance score (KPS, from 10 to 100%)[24] and the Cooperative Oncology Group Performance Status scale (ECOG-PS, from 0 to 4)[25,26]. The evaluation time took, on average, 15 (range 11-18) minutes.

The patient and tumor characteristics, SEER and TNM staging, therapeutic options, and death causes during the follow-up were recorded. Tumors were classified according to the TNM-classification of the UICC, 7th edition 2009. MDM decisions were based on CM-CHUSJ written protocols that follow national and international standards.

In our study, we defined undertreatment 1) when the patient refused the MDM proposal, 2) when, due to intolerance, it was not possible to complete the treatment defined in the MDM, and 3) when a standard treatment was not proposed in the MDM given the advanced chronological age or limiting physiological vulnerability.

Statistical analysis

For continuous variables, normality was assessed by Shapiro-Wilks or Kolmogorov-Smirnov tests and by visual inspection of the data distribution. If normally distributed, the results were summarized by the mean and standard deviation; otherwise, the

median and the interquartile range was used. Student's t-test assessed the differences of the independent variables between the two groups (standard treatment and undertreatment) once normality was demonstrated; otherwise, the Wilcoxon rank-sum test was applied. Absolute (n) and relative (%) frequencies were reported for the categorical variables. The Chi-square test and Fisher's exact test assessed the association between the independent categorical variables and the defined groups. Propensity score matching (PSM) was used to reduce covariates' bias, such as frailty, SEER, and TNM scores on assessing the effect of treatment on survival. Survival analyses were performed using Cox proportional hazards models and the Kaplan-Meier method. All statistical analyses were performed using the *survminer* (version 0.43.1) and *survival* (version 2.43.3) packages in R (version 3.5.3) (R Core Team 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

Our observational study included 92 patients (one male), which represented 26.1% of the new BC cases treated at CM-CHUSJ in 2014. The median age was 77 (range 70-94) years.

Forty-four (47.8%) were widows, and forty-two (45.7%) were married. Most (74.0%) either had no education or attended primary school, and 12.0% had a university degree. Seventy (76.1%) patients agreed to answer sociodemographic, psychological, and ADLs questionnaires: thirty-three patients (47.1%) reported feeling "younger" than they were; sixty-four (91.4%) mentioned having a "taste for life"; half lived with her husband and 15.7% lived alone; most patients (77.1%) assessed themselves as autonomous without any need for support from family members; thirty-two patients (45.7%) were completely independent in their ADLs, and 28.6% had only mild dependence. We assessed the occurrence of falls in the last year, one of the first indicators of frailty. Fifty (71.4%) had not suffered any fall; however, half of them emphasized that they were "afraid of falling". In the psychological assessment, most patients (71.4%) were classified as healthy, and 15.7% were depressed (Appendix A).

Sixty-two (67.4%) patients agreed to undergo a geriatric evaluation. The categorization of frailty on the 3 scales was discordant (G8: 41.9%, fTRST: 74.2%, GFI: 32.3%). We also applied the traditional functional scales, illustrating their higher agreement (ECOG-PS 0: 45.7%, KPS 90-100%: 47.8%) (Appendix B).

Most patients presented with a palpable mass (73.9%) detected by the patient or by a family member during hygiene care. In 2 patients, the diagnosis was made during the study of symptomatic metastatic bone disease. Surveillance imaging exams detected only 23.9%, and of these, only one patient was referred from the mass screening program (Appendix B).

There was a predominance of stage IA (27.2%) and IIA (26.1%) in TNM staging, in contrast to 6.5% in stage 0 and 7.6% in stage IV. Using the SEER summary staging system to classify our invasive tumors leads to an unexpectedly similar distribution between local (48.8%) and regional disease (43.1%). Concerning invasive tumors, the predominant histological subtype was "no special type" (75.6%); the Bloom-Richardson grading was evenly distributed (33.7% were G3, 39.5% G2, and 26.7% G1), and lymphovascular invasion was present in 31.4%. Regarding immunohistochemistry (IHC), 83.0% were ER positive, 71.0% PR positive, and 11 tumors (12.8%) were HER2 positive. Concerning molecular classification, 82.6% had luminal-*like* tumors, 5.8% were HER2 enriched, and 11.6% were triple-negative (TN). A

more specific subdivision of luminal tumors was not possible as HER2 status was not studied in 18, nor was Ki67 in 16 cases.

Eighteen patients (19.6%) were referred to genetic counseling: the man, 8 women with previous contralateral tumors, 5 with bilateral synchronous tumors, 3 with suggestive family history, and one with previous ovarian cancer. Only one patient was BRCA2 positive.

The MDM decision-making was consensual in 61 patients (66.3%) but controversial and adapted in 31 patients (33.7%), due to frailty in 18 and advanced chronological age in 13. One patient, the only male, refused any kind of treatment. Seventy-four (80.4%) patients were submitted to surgery (55.4% underwent BCS) and eighteen (19.6%) patients were not operated. Of these, 15 (16.3%) patients underwent primary endocrine therapy (PET): 4 refused surgery and 11 had no physiological conditions. Seven (7.6%) patients underwent neoadjuvant chemotherapy, and 2 of them – with stage IV Luminal B-HER2 positive tumors – were not proposed for surgery afterward. Of the 68 patients with invasive tumors submitted to surgery, only 2 frail patients (aged 90 and 83) with TN tumors were not proposed for adjuvant treatment. The remainder were submitted to various combinations of adjuvant treatment: 55 (80.9%) to endocrine therapy, 46 (67.6%) to radiotherapy, 21 (30.9%) to chemotherapy, and 9 (13.2%) to trastuzumab.

According to our pre-specified definition, 49 patients (53.3%) were undertreated (Appendix C, D). KPS and ECOG-PS showed a significant difference between undertreatment and standard treatment groups. Conversely, the chronological age, the three frailty screening tools applied, and comorbidities were not associated with the treatment outcomes. Regarding the diagnosis and staging (TNM and SEER), we found a significant difference between undertreatment and standard treatment groups. Analyzing by molecular subtypes, no relevant difference was found regarding undertreatment, probably due to its inaccurate classification (Table 1).

Our patients´ overall 5-year survival was 66.1% [95% CI: 57.0%, 76.5%] (Appendix E). Thirty-three (35.9%) patients died; fifteen (45.5%) due to BC, most with M1 bone plus visceral disease (Appendix C). Eighteen (54.5%) died from a non-cancer cause; however, four of these (22.2%) had stable M1 disease. Of the 33 patients who died, 27 (81.8%) were undertreated in contrast to the 52 patients alive without any evidence of oncological disease at the end of the follow-up, in which only 30.8% were undertreated. No significant differences in survival status were found when comparing death from all causes and death from BC (Appendix F). Thus, the vital status was aggregated.

A relevant finding was the undertreatment impact on 5-year survival stratified by the type of cancer treatment (HR=5.1 [95% CI: 2.1-12.5])(Figure 1). Our undertreated patients had an overall 5-year mortality rate of 55.1% (and 24.5% of cancer lethality rate) in contrast to the standard treatment group, in which the overall 5-year mortality rate was only 13.9% and 7.0% of cancer lethality rate. To mitigate the contribution of frailty on the overall survival status, a propensity score matching of patients using frailty scores highlights the worse prognosis for the undertreatment group (HR=9.3 [95% CI: 2.7-32.0])(Figure 2). A subanalysis regarding the omission of surgical treatment showed a significant association with undertreatment well supported by the clear negative impact on survival – held, even after frailty-matching of non-operated patients (Figure 3,4).

DISCUSSION

The definition of geriatric age should consider chronological age, biological age, social role change, or functional capacities. We used (as stated by SIOG, EORTC, or NCCN) the 70 years' cut-off, but this landmark lack consensus [3,7,8,11,16,38].

Half of our patients have good self-perceived health. Indeed, the question in the G8 tool[21] – "*in comparison with other people of the same age, how does the patient consider her health status"* – reported that 51.6% considered their health status to be as good or better than other ones. This figure is in-line with the 49.7% healthy EU population aged 65-74 with good self-perceived health in a recent ageing study [3]. Therefore, we can consider that our patients are resilient: 91.4% like to live, 71.4% have not suffered any fall, 47.1% feel younger than their chronological age, and 45.7% were completely independent in their ADLs and ECOG-PS 0. The ability to translate this resilience into daily practice – the mirror-image of frailty – with a more positive connotation, more than a taxonomic debate, allows us to refocus on a subgroup of fit patients and to provide them a better MDM guidance [28,34].

Contrary to the current (screening-driven) trend in BC diagnosis, we found a late diagnosis mostly clinically based. As in other studies, only 23.9% of patients were diagnosed with periodic surveillance imaging, explaining why only 6.5% of DCIS were observed (instead of the expected 16-18%)[5,41,42]. Given the mentioned generational change, it is time to offer women over 70 years the mass mammography screening since some studies showed a survival benefit for older women with a life expectancy of more than 10 years [40]. A late diagnosis consequence was a more advanced TNM staging (51.2% were N+). Indeed, this is clear through the SEER summary staging applied to our invasive tumors: 48.8% had local disease (instead of the expected 64%) and 43.1% regional disease (more than the estimated 27%)[5]. More evident is our worst 5-year overall survival - excluding the HER2 enriched tumors - comparing to all-ages 2019-2020 ACS statistics (Table 2). Contrary to other studies [13,42], a more favorable tumor biology was not found (33.7% were G3 and 31.4% had lymphovascular invasion), which, on top of an incomplete IHC study (HER2 missing in 20.9% due to an advanced age preconceived intention-not-to-treat) might constrain the MDM decision causing a worse prognosis.

The best BC diagnostic and treatment strategy in older women remains challenging to define [7,10,13,16,27,47]. Likewise, the definition and mainly the clinical impact assessment of BC undertreatment is also elusive as it involves more than one and sequential therapeutic modalities [16,18,27,44,45]. The key question is whether we can tailor the treatment, knowing the physiological reserve, comorbidities,

vulnerabilities, and patient will. The geriatric evaluation performed and the explanation of its goals allowed to create a time-consuming, difficult-to-measure but rewarding open discussion with our patients about their cancer diagnosis and the risk-benefits of their treatments that will provide proper support to MDM therapeutic management [27,33,38]. There are several geriatric tools and strategies recommended in the literature [29-39]. A geriatric comprehensive assessment was not yet carried out by us in 2014. The G8 screening tool - chosen for EORTC trials [16] - consensually emerged as a good predictor of geriatric risk and overall survival [37]. As seen in other studies [31], the categorization of frailty in the three applied screening tools was discordant, and none of them showed an association with undertreatment.

Age is a proven independent risk-factor for non-standard BC treatment [7,10,30,39]. A significant, albeit variable, amount (in some studies well above 50%) of older adults with BC are undertreated [13,44-46]. In our cohort it represented 53.3%. Our study's key answer is whether age-related BC undertreatment is itself a determinant cause of a worst 5-year survival or a consequence of a limiting fragility. Co-morbid illnesses and functional status probably influence more older patients' life expectancy than the BC itself [27]. Age, frailty, and comorbidities are non-modifiable risk-factors that predict overall mortality. On the other hand, tumor biology and TNM stage are modifiable risk factors for cancer lethality. We clearly show a negative impact of BC undertreatment - independent of frailty - on 5-year survival (Figure 1,2). An unfit older patient with a luminal BC and a short life expectancy is adequately treated with PET. Surgery in these patients will offer better local control but probably has no impact on overall survival. Instead, fit older adults must undergo a standard treatment to avoid shortening their life expectancy [30,44]. An unproven survival benefit of the different therapeutic modalities due to ageing idiosyncrasies does not allow an accurate prognosis evaluation in older patients [41-47]. Despite the variability of our cohort [48,49], we show a frailty-independent negative impact of the omission of surgery on 5-year survival (Figure 3,4).

Our study's main limitations are the small sample size, the incomplete IHC characterization, single-center study, and the lack of a formal assessment of patient-reported outcomes or health-related quality of life. As for strengths, we emphasize being a real-world study with complete clinical data, a resilient cohort with no loss to 5-year follow-up, and all causes of death verified.

CONCLUSION

The BC treatment in older adults must be individualized. An assumed more favourable tumor-biology disease in a heterogeneous age subgroup is currently treated without the support of RCT evidence-based recommendations.

In our study, we did not find a low-risk disease; the BC diagnosis was late (mainly based on self-examination), contributing to worse prognosis (only 6.5% of DCIS, 51.2% of the invasive tumors were N+, 33.7% were G3, and 8.1% M1). The prevalence of frailty in the applied screening tools was discordant (G8: 41.9%, fTRST: 74.2%, GFI: 32.3%), and most of the studied patients showed resilience.

In older women, BC treatment more than assessing the frailty for treatment conditioning; it is essential to know the physiological reserve and the patient's well-informed willingness to be treated. In older patients, the concept and the clinical impact of undertreatment remain difficult to establish. We found a considerable proportion (53.3%) of undertreatment with a significant negative impact on 5-year survival independent of frailty. Moreover, we show a frailty-independent positive impact of surgical treatment on overall survival.

Time and dedication to an integrated geriatric evaluation and good clinical communication to assess the risk-benefit profile are essential for older adults centered-care and appropriate oncologic decision-making that minimize undertreatment and avoid its potential adverse impact on survival.

DECLARATIONS:

Abbreviations

ACS: American Cancer Society; ADL: activities of daily living; BC: breast cancer; BCS: breast conservative surgery; CI: confidence interval; CM-CHSU: Breast Center of São João University Hospital; DCIS: ductal carcinoma in situ; ECOG-PS: Cooperative Oncology Group Performance Status scale; EORTC: European Organisation for Research and Treatment of Cancer; ER: Estrogen receptor; EU: European Union; fTRST: Flemish version of the Triage Risk Screening Tool; G8: Geriatric 8 screening tool; GFI: Groningen Frailty Indicator; HER2: human epidermal growth factor receptor-2; HR: hazard ratio; IHC: immunohistochemistry; Ki-67: proliferation index marker; KPS: Karnofsky performance score; MDM: multidisciplinary meeting; NCCN: National Comprehensive Cancer Network; PET: primary endocrine therapy; PR: Progesterone receptor; RCT: randomized controlled trials; SEER: Surveillance, Epidemiology, and End Results Program; SIOG: International Society of Geriatric Oncology; TN: triple negative; TNM: Classification of Malignant Tumors; USA: United States of America.

Ethics approval and consent to participate

The study *("Geriatric evaluation in older patients with breast cancer – a clinical pathway validation")* was performed in accordance with the ethics international guidelines and approved by the Ethics Committee of São João University Hospital on June 28th 2013 (CES 111-13). Written study information was provided and a written informed consent was obtained from all participants. The study enrolment took place during 2014.

Consent for publication

Not applicable

Availability of data and materials

All relevant data analyzed during this study are included in this published article and additional tables and figures are available as supplementary material. Other data requests can be submitted to the corresponding author.

Competing interests

All authors declare that they have no competing interests.

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Authors´ contributions

FO, BP, ASB, JLF and AL-M defined the study design. FO, ARB and JU made the data acquisition. ASB and BP defined the statistical analysis. ASB prepared the figures and tables. FO, BP and ASB wrote the manuscript. All authors reviewed and approved the submitted manuscript. All authors shared the decision to submit the paper for publication.

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Table 1. Patient's characteristics

Characteristic[1]	Overall, N = 92	N	Standard treatment, N = 43	Undertreatment, N = 49	p-value[2]
5Y Follow-up status		92			< 0.001
Alive	59 (64%)		37 (86%)	22 (45%)	
Dead	33 (36%)		6 (14%)	27 (55%)	
Age	77 (73, 83)	92	76 (72, 80)	78 (74, 85)	0.056
Diagnosis		92			0.003
Imaging	21 (23%)		16 (37%)	5 (10%)	
Mass screening	1 (1.1%)		0 (0%)	1 (2.0%)	
Self-examination	68 (74%)		27 (63%)	41 (84%)	
Symptomatic M1 disease	2 (2.2%)		0 (0%)	2 (4.1%)	
KPS		92			< 0.001
90 – 100	44 (48%)		30 (70%)	14 (29%)	
70 – 80	19 (21%)		9 (21%)	10 (20%)	
50 – 60	23 (25%)		4 (9.3%)	19 (39%)	
30 – 40	6 (6.5%)		0 (0%)	6 (12%)	
ECOG-PS		92			0.044
0	42 (46%)		27 (63%)	15 (31%)	
1	27 (29%)		12 (28%)	15 (31%)	
2	11 (12%)		3 (7.0%)	8 (16%)	
3	11 (12%)		1 (2.3%)	10 (20%)	
4	1 (1.1%)		0 (0%)	1 (2.0%)	
G8		62			0.9
Fit	36 (58%)		23 (72%)	13 (43%)	
Frail	26 (42%)		9 (28%)	17 (57%)	
fTRST		62			0.9
Fit	16 (26%)		9 (28%)	7 (23%)	
Frail	46 (74%)		23 (72%)	23 (77%)	
GFI		62			0.12
Fit	42 (68%)		25 (78%)	17 (57%)	
Frail	20 (32%)		7 (22%)	13 (43%)	
Comorbidities		92			0.2
1	11 (12%)		6 (14%)	5 (10%)	
2	21 (23%)		13 (30%)	8 (16%)	
3	25 (27%)		12 (28%)	13 (27%)	
4+	35 (38%)		12 (28%)	23 (47%)	
Bloom and Richardson grading		86			0.012
Grade 1	23 (27%)		15 (41%)	8 (16%)	
Grade 2	34 (40%)		15 (41%)	19 (39%)	
Grade 3	29 (34%)		7 (19%)	22 (45%)	
SEER Summary Stage system		92			< 0.001
In situ	6 (6.5%)		6 (14%)	0 (0%)	
Local stage	42 (46%)		24 (56%)	18 (37%)	
Regional stage	37 (40%)		13 (30%)	24 (49%)	
Distant stage	7 (7.6%)		0 (0%)	7 (14%)	
TNM stage		92			< 0.001
Stage 0	6 (6.5%)		6 (14%)	0 (0%)	
Stage I	29 (32%)		20 (47%)	9 (18%)	

Stage II	33 (36%)		14 (33%)	19 (39%)	
Stage III	17 (18%)		17 (18%)	3 (7.0%)	
Stage IV	7 (7.6)		0 (0%)	7 (14%)	
Molecular-like classification		86			0.7
Luminal	47 (55%)		23 (62%)	24 (49%)	
Luminal_HER2_missing	18 (21%)		7 (19%)	11 (22%)	
Luminal_HER2 positive	6 (7.0%)		1 (2.7%)	5 (10%)	
HER2-enriched	5 (5.8%)		2 (5.4%)	3 (6.1%)	
Triple Negative	10 (12%)		4 (11%)	6 (12%)	
Surgery		92			< 0.001
No	18 (20%)		0 (0%)	18 (37%)	
Yes	74 (80%)		43 (100%)	31 (63%)	

[1]Statistics presented: n (%); median (IQR)

[2]Statistical tests performed chi-square test of independence; Wilcoxon rank-sum test; Fisher’s exact test

Table 2. Comparison of our data with all ages ACS BC Facts & Figures 2019-2020

	n (%)	*ACS %*	5Y-survival	*ACS 5Y-survival*
Local disease	42 (48.8%)	*64%*	76.2%	*99%*
Regional disease	37 (43.1%)	*27%*	56.8%	*86%*
Distant disease	7 (8.1%)	*6%*	14.3%	*27%*
RH+ HER2-	47 (54.6%)	*73%*	63.8%	*92%*
RH+ HER2 missing	18 (25.4%	-	50.0%	-
RH+ HER2+	6 (7.0%)	*11%*	83.3%	*89%*
RH- HER2-	10 (11.6%)	*12%*	50.0%	*77%*
RH- HER2+	5 (5.8%)	*4%*	100%	*83%*

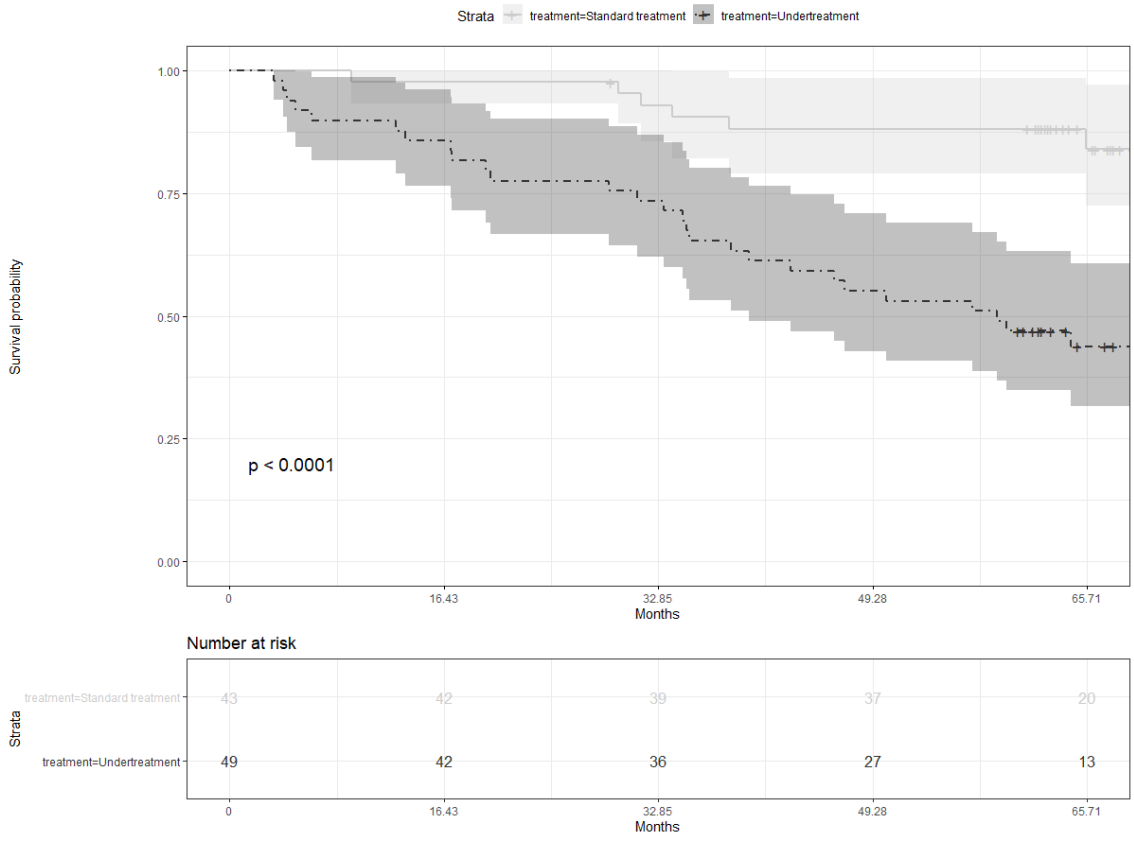

Figure 1. Kaplan Meier survival curve. HR for undertreatment [95% CI] = **5.1** [2.1 – 12.5]

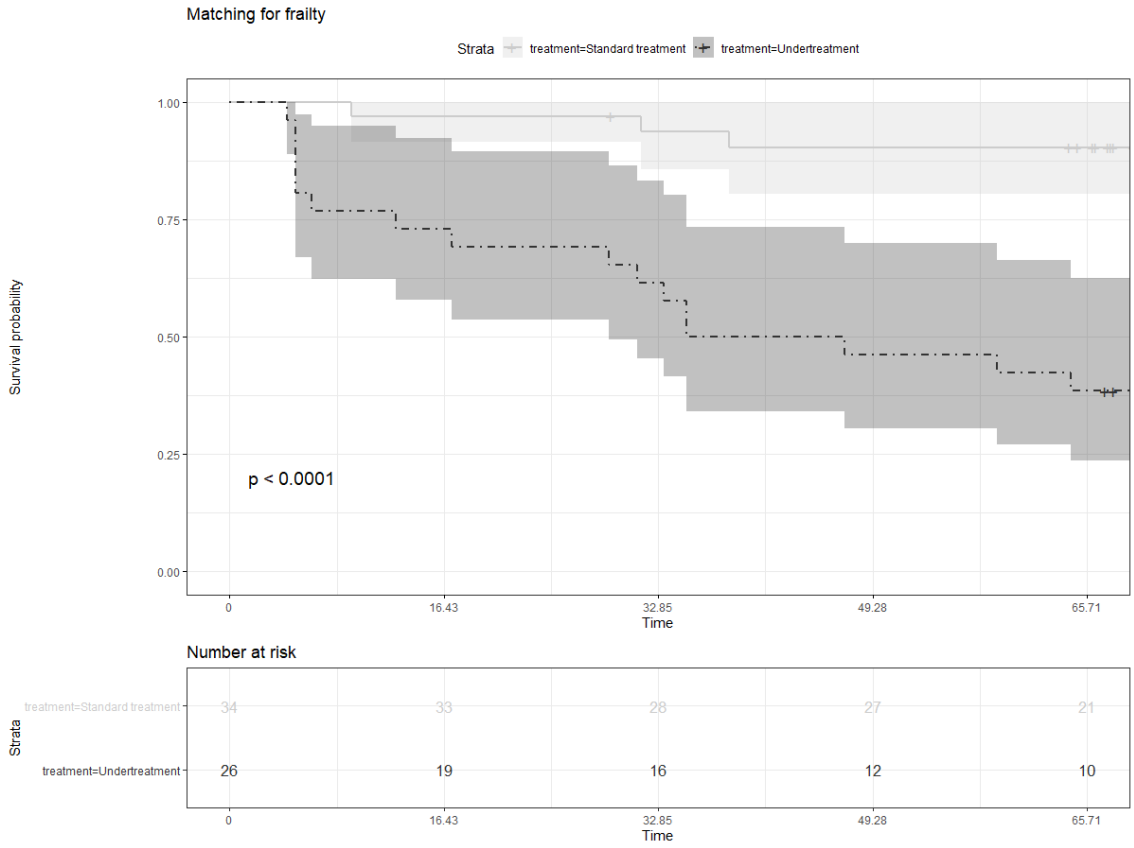

Figure 2. Kaplan Meier survival curve (matched for frailty). HR for undertreatment [95% CI] = **9.3** [2.7 – 32.0].

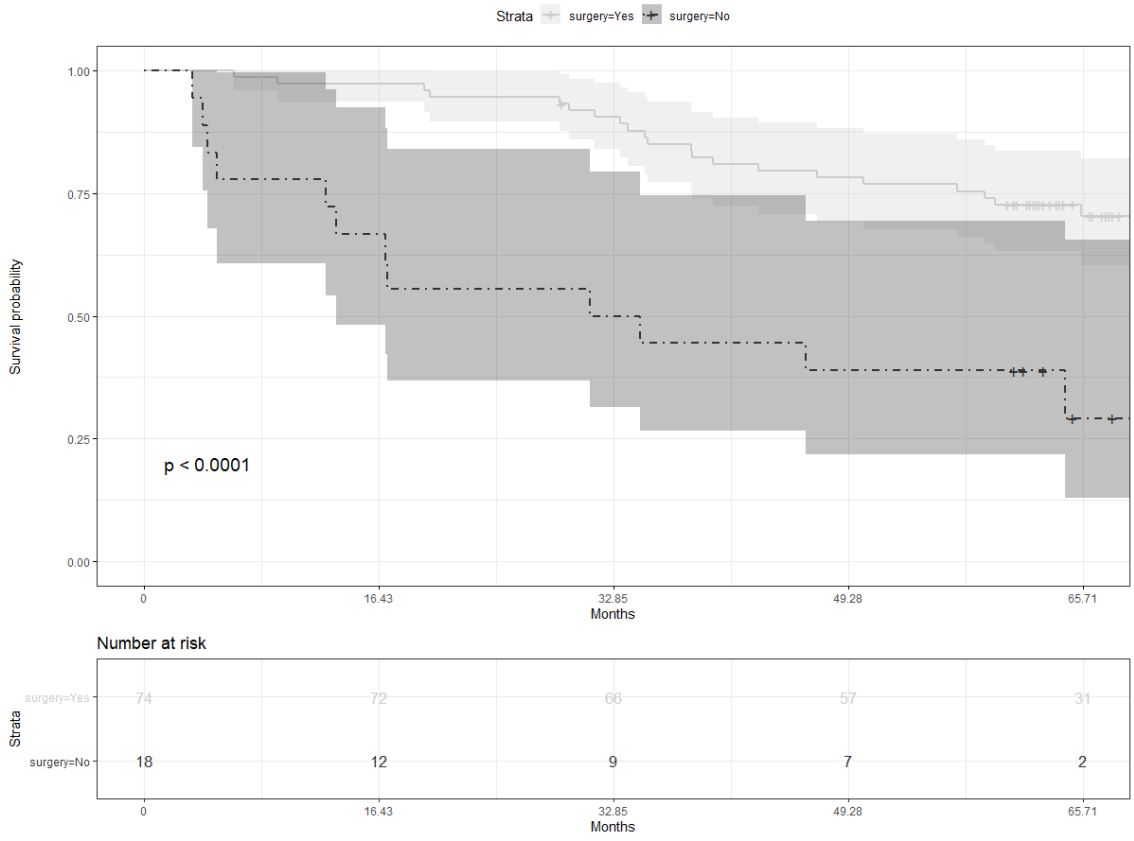

Figure 3. Kaplan Meier survival curve. HR for omission of surgery [95% CI] = **3.9** [1.9 – 7.9]

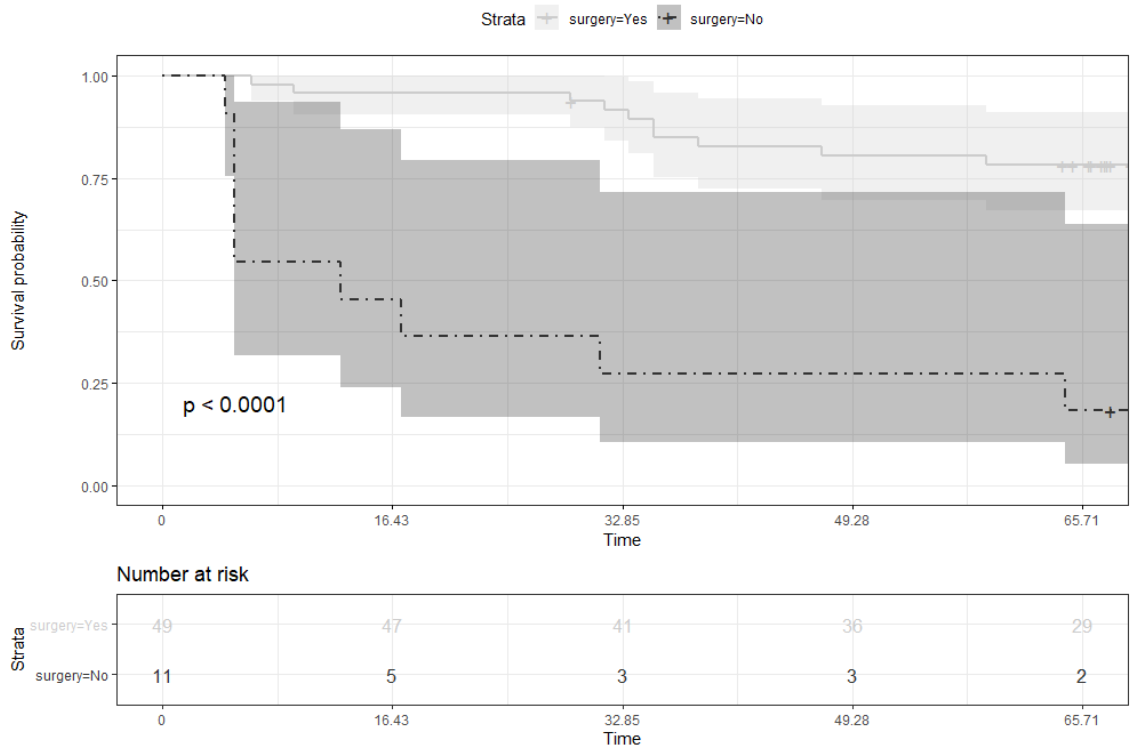

Figure 4. Kaplan Meier survival curve (matched for frailty). HR for omission of surgery [95% CI] = **8.2** [3.3 - 20.1]

Figures

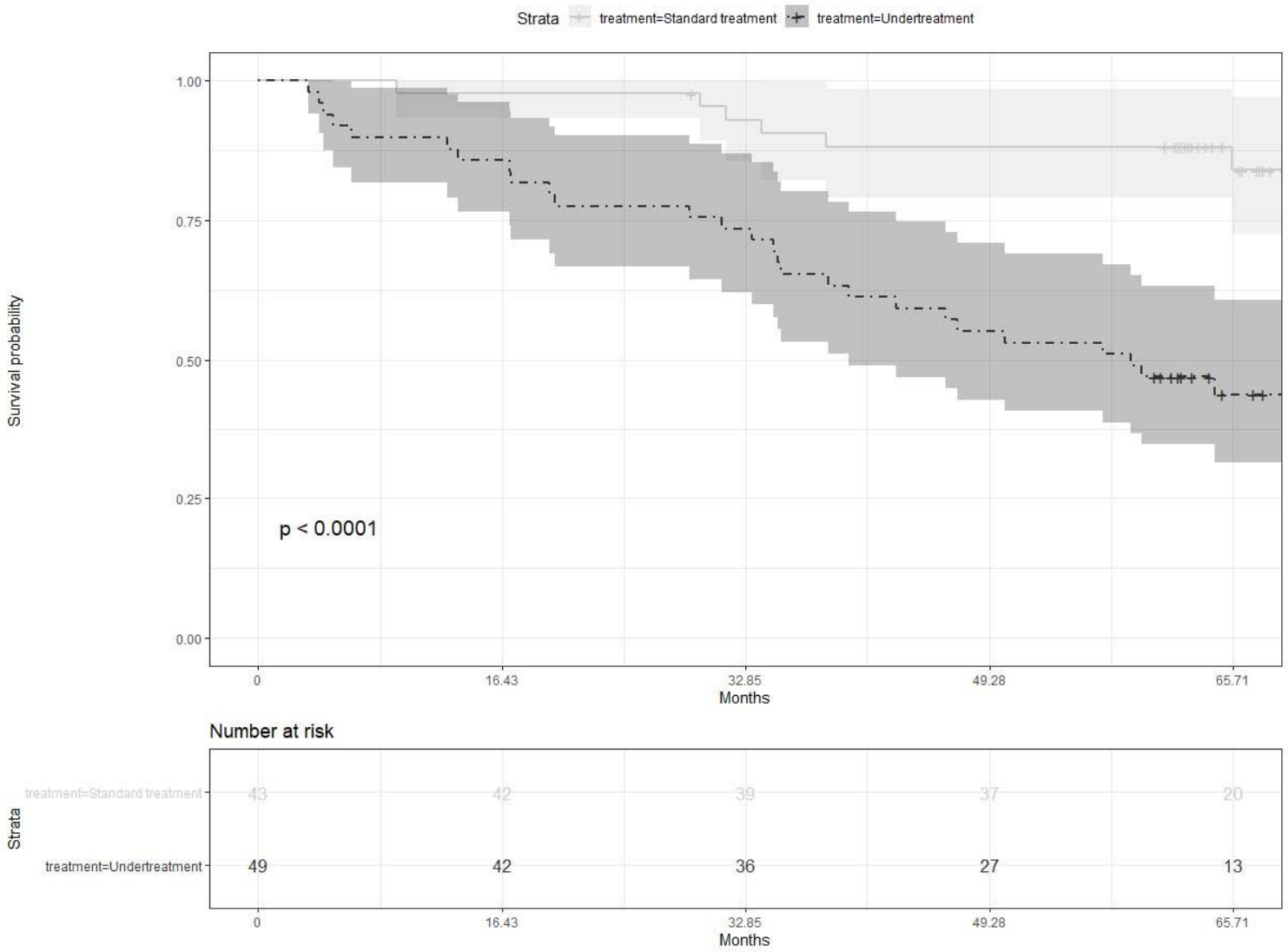

Figure 1

Kaplan Meier survival curve. HR for undertreatment [95% CI] = 5.1 [2.1 – 12.5]

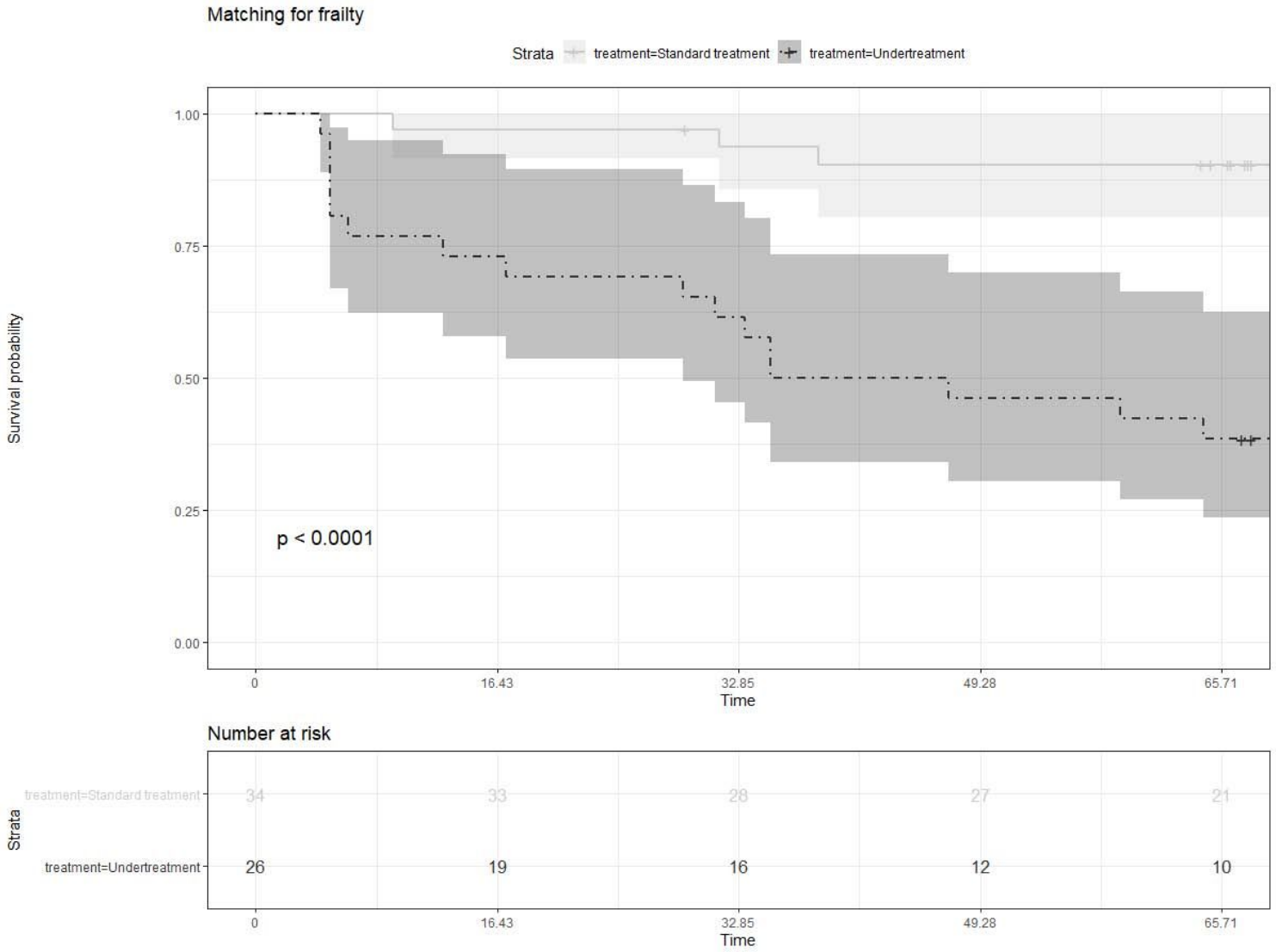

Figure 2

Kaplan Meier survival curve (matched for frailty). HR for undertreatment [95% CI] = 9.3 [2.7 – 32.0].

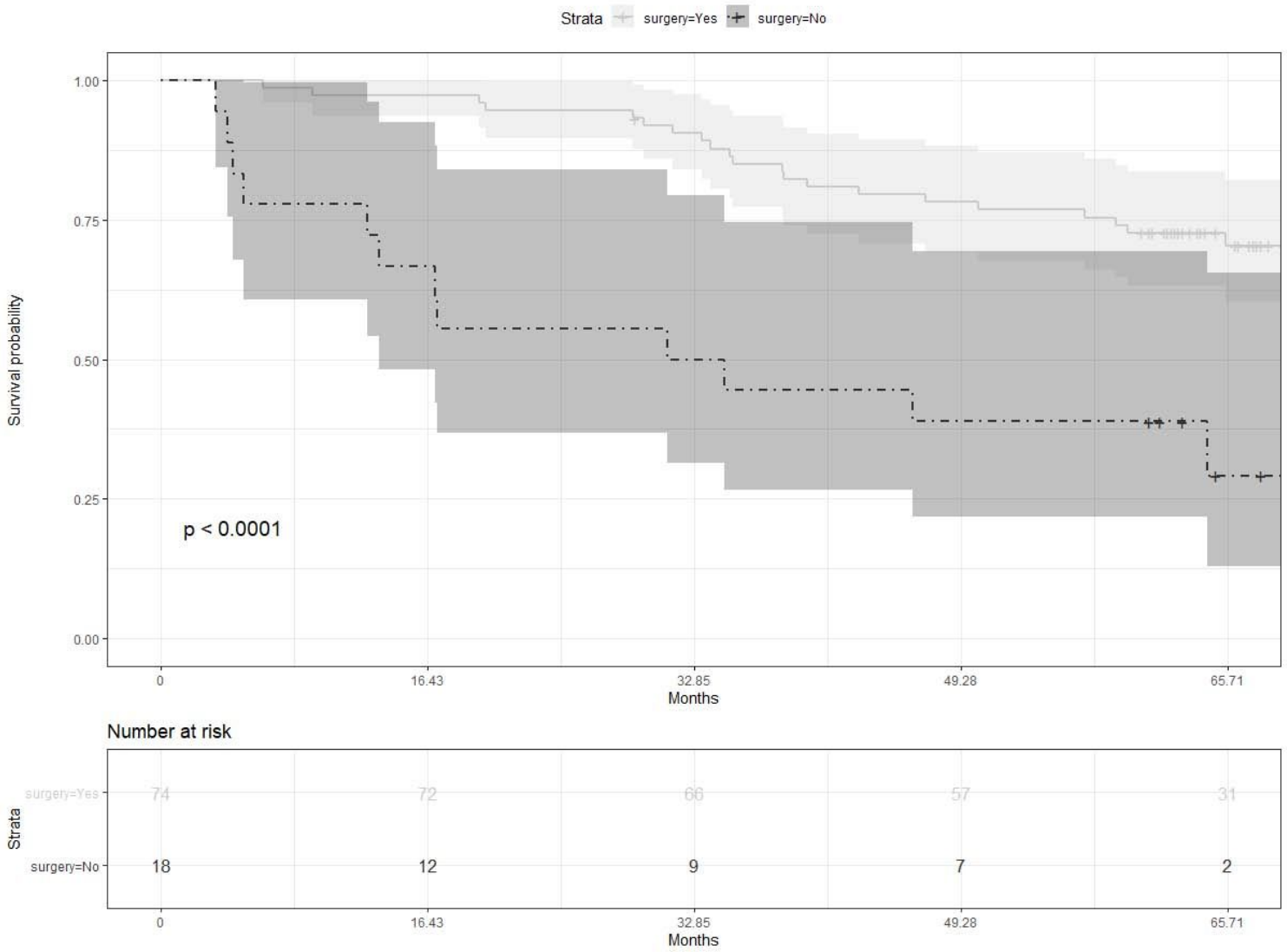

Figure 3

Kaplan Meier survival curve. HR for omission of surgery [95% CI] = 3.9 [1.9 – 7.9]

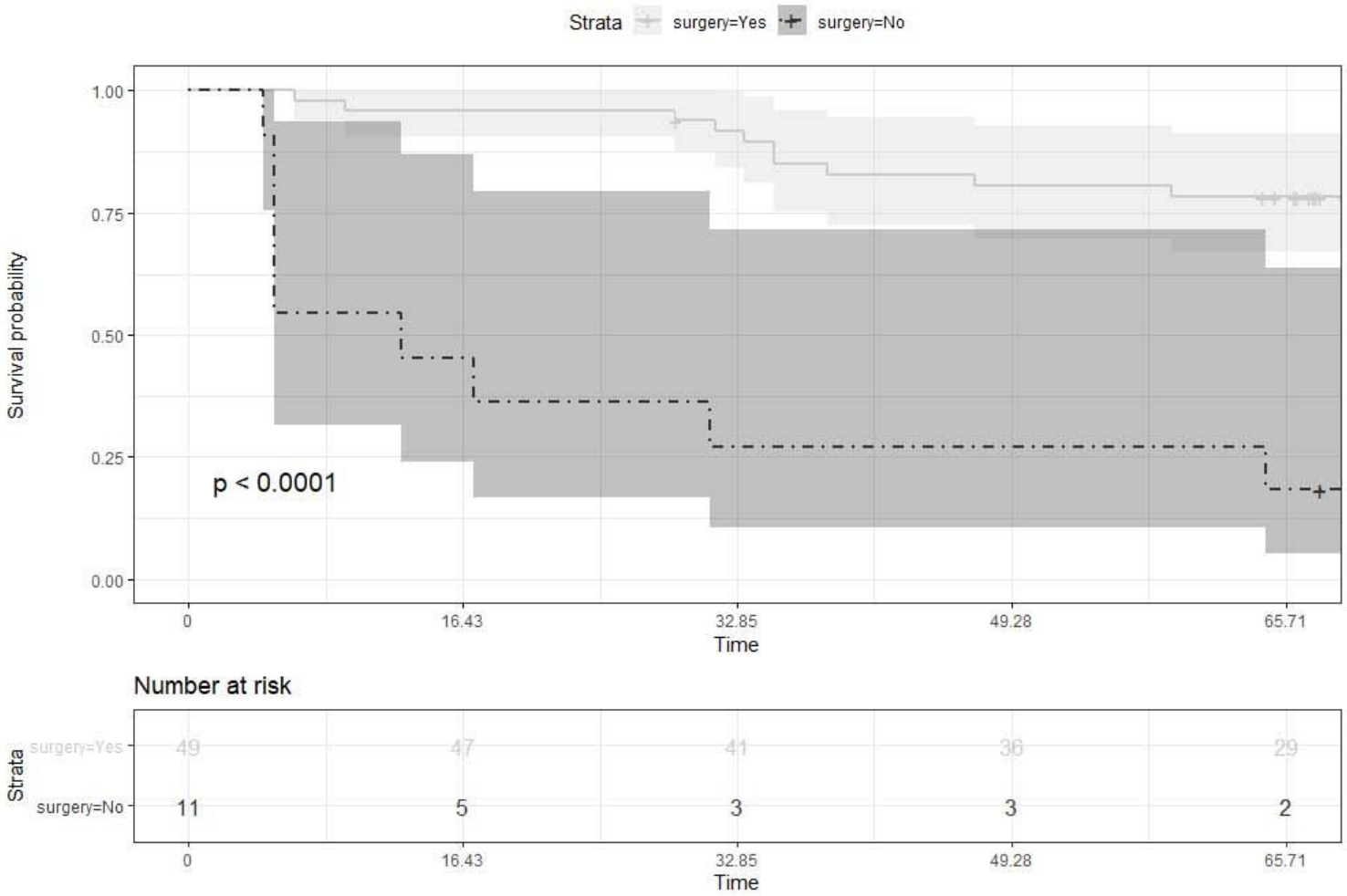

Figure 4

Kaplan Meier survival curve (matched for frailty). HR for omission of surgery [95% CI] = 8.2 [3.3 - 20.1]

Supplementary Files

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- Supplementarymaterial.pdf