1. Final Study Report [EDINBURGH EBC – Pangaea # 2019-9068]

A Real World Retrospective Study of Clinical Characteristics and Treatment Patterns of Early Breast Cancer Patients in Scotland

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Observational Study Final Report Electronically Signed and Approved by Lilly: approval date will be provided

Abstract

Background: Despite adjuvant endocrine treatment (AET) advances, hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−), node-positive early breast cancer (EBC) is associated with a considerable (~20%) risk of recurrence. We conducted a retrospective study to describe demographic/clinical characteristics and outcomes alongside treatment patterns in patients (pts) with HR+, HER2− node-positive EBC in the region of Scotland served by the Edinburgh Cancer Centre, a specialist referral centre.

Methods: National Health Service Lothian data sources were utilized. Included were all adult pts diagnosed with HR+, HER2− node-positive EBC between 1/1/05–31/12/20, commencing AET within 16 months of definitive surgery, with follow-up until 1/8/21; pts treated with abemaciclib within the monarchE trial were excluded. Analysis focused on pts with high risk factors (HRisk), i.e., ≥4 pathologically positive ipsilateral axillary lymph nodes (ALNs) or 1–3 pALNs plus either tumour size ≥5cm and/or histological grade 3 (G3), in line with high risk factors for most (91%) of the pts in the monarchE trial.

Results: Overall, 4600 pts were identified (HRisk n=1498, 33%). In the HRisk group, 16% received neoadjuvant chemotherapy, 66% adjuvant chemotherapy and 92% radiotherapy; AET mostly involved letrozole (34%). Invasive Disease-Free Survival (IDFS) in the HRisk group was 76% and 56% at 5 and 10 years. For pts with 1-3 pALNs, 5-year IDFS and Overall Survival (OS) were adversely affected by HRisk status (tumour ≥5cm and/or G3) and were similar to the 5-year IDFS and OS of pts with 4-9 ALNs. For pts with HRisk disease, both IDFS and OS were adversely affected by postmenopausal status and ≥10 ALNs (Table 1).

Conclusions: Real world data from the Lothian region of Scotland confirm that a considerable proportion of HR+, HER2− node positive EBC represents HRisk disease associated with worse outcomes, pointing to a need for improved treatments.

Table 1. IDFS and OS in HRisk group (baseline)

	3y IDFS %	5y IDFS %	3y OS %	5y OS %
Overall (n=1498)	87	76	91	81
No of pALNs (n=1125)				
1-3 (n=539)*	88	79	92	82
4-9 (n=393)	88	77	91	82
≥10 (n=193)	79	67	88	73
Menopausal status (n=1498)				
Pre/Peri (n=410)	90	82	95	88
Post (n=1071)	85	74	89	78

*Tumour ≥5cm and/or G3

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A Real World Retrospective Study of Clinical Characteristics and Treatment Patterns of Early Breast Cancer Patients in Scotland

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Glossary

ACT: Adjuvant Chemotherapy
AET: Adjuvant Endocrine Treatment
ALN: Axillary Lymph Nodes
AJCC: American Joint Committee on Cancer
CHIs: Community Health Index
CDK: Cyclin-Dependent Kinase
EBC: Early Breast Cancer
ECOG: Eastern Cooperative Oncology Group
ET: Endocrine Therapy
ER: Estrogen Receptor
HER2: human epidermal growth factor receptor 2
HR: hormone receptor
HRisk: High Risk
Non-HRisk: Non-High Right
IDFS: Invasive Disease-Free Survival
IIBTR: Ipsilateral invasive breast tumour recurrence
NACT: Neoadjuvant chemotherapy
NHS: National Health Service
OS: Overall Survival
PR: Progesterone Receptor
QPI: Quality Performance Indicator
RWE: Real World Evidence
SACT: Systemic Anti-Cancer Therapies
SCAN: South East Scotland Cancer Network
SESCD: South East Scotland Database
SIMD: Scottish Index of Multiple Deprivation
SLNB: Sentinel Lymph Node Biopsy
TNM: Tumour size, Node, Metastasis
WLE: Wide Local Excision

3. Rationale and background

Breast cancer is the most common cancer in the UK accounting for 15% of all new cancer cases (1). Most patients (90%) are diagnosed at an early stage of their disease (EBC). The most prevalent breast cancer subtype is the hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) which accounts for approximately 70% of all breast cancers (2). These patients are treated with curative intent with a combination of surgery, radiotherapy, adjuvant/neoadjuvant chemotherapy, and adjuvant endocrine therapy (AET) depending on the individual risk of relapse and predicted sensitivity to systemic therapies.

In the last two decades there have been very few advances in the adjuvant treatment of HR+ HER2- breast cancer. The use of aromatase inhibitors and the extended duration of therapy have led to improvements in patients' outcomes associated with adjuvant endocrine therapy, yet there remains a considerable risk of disease recurrence that extends over a long period of time (3).

CDK-4/6 inhibitors, combined with endocrine therapy, have demonstrated a clinical benefit improving survival in patients with advanced/metastatic HR+ breast cancer (4-9). In the adjuvant setting, the phase III randomised monarchE trial met its primary end point at a pre-planned interim analysis. In this study, the combination of adjuvant Abemaciclib for two years with endocrine therapy improved the Invasive Disease Free Survival (IDFS) compared to adjuvant endocrine therapy alone in patients with high risk HR+ HER2- EBC patients. High risk was identified as ≥4 pathologically positive axillary lymph nodes (ALNs) or, 1-3 pathologically positive ALNs with at least one additional risk factor including a primary invasive tumour size of ≥ 5cm, a tumour with a histological grade of 3 or a central proliferation index (Ki67) of ≥ 20% (10).

We aim to describe the demographics, clinical characteristics and long term outcomes, alongside treatment patterns in patients with or without monarchE-like EBC tumour risk profile, on historic standard of care for EBC patients in a real-world setting in Scotland.

4. Research question and objectives

4.1 Primary Objective

The main objective of this study is to describe the patient profile, demographics and clinical characteristics of early breast cancer patients in South East Scotland by high (HRisk) and non-high risk (non-HRisk) according to monarchE criteria .

4.2 Secondary Objectives

Among early breast cancer patients, the secondary objectives of this study are to:

- Describe the treatment patterns specific to early breast cancer patients, including: surgery, radiotherapy, chemotherapy, endocrine treatment and targeted treatment.
- Describe reasons for discontinuation of treatment.
- Describe the frequency of Oncotype Dx (Genomic profiling test) and the clinical and patient characteristics of those tested.
- Estimate survival (IDFS and OS) without recurrence for different treatment modalities at follow up (e.g. at 12, 24 and 36, 48, 60 and 120 months).
- Estimate the healthcare resource utilisation, for example, frequency of hospital visits (inpatient, outpatient) and length of stay.

4.3 Exploratory Objectives

N/A

5. Research Design

5.1 Study design

A retrospective cohort study design was used. All records of men and women with primary invasive breast cancer diagnosed (Incidence date in Cancer Registry) from 1 January 2005 to 31 December 2020, with follow-up until 1st August 2021.

Men and women with first breast cancer, aged 18 and over, were identified based on the most recent chronological record of diagnosis code (Cancer Registry incidence) ICD-10 C50.X for the unique patient identifier. In the case of multiple simultaneous records (duplicates or multiple same-date cancer), the record with the most complete data and highest risk disease factors were selected.

Patients identified as HR+ and HER2-. HER2- is defined as HER2 0 or 1+ by immunohistochemistry (IHC) or 2+ and not amplified on FISH. HR positive defined as either/or Estrogen (ER) / Progesterone (PR) positive, where positive is Allred score >2. ER/PR low is Allred score of 3 or 4 and were also included as a subgroup of the study population.

This analysis was performed on the National Health Service (NHS) Lothian data collected from several sources, including SMR06 Cancer Registration, SMR01 Inpatients/Outpatients, Quality Performance Indicator (QPI) audits, Chemocare and the South East Scotland Cancer Database (Section 6.5). It included the assessment of the different treatment lines, the use of the genomic profiling test Oncotype DX, survival for up to 15 years, treatment durations and healthcare utilisation.

5.2 Setting

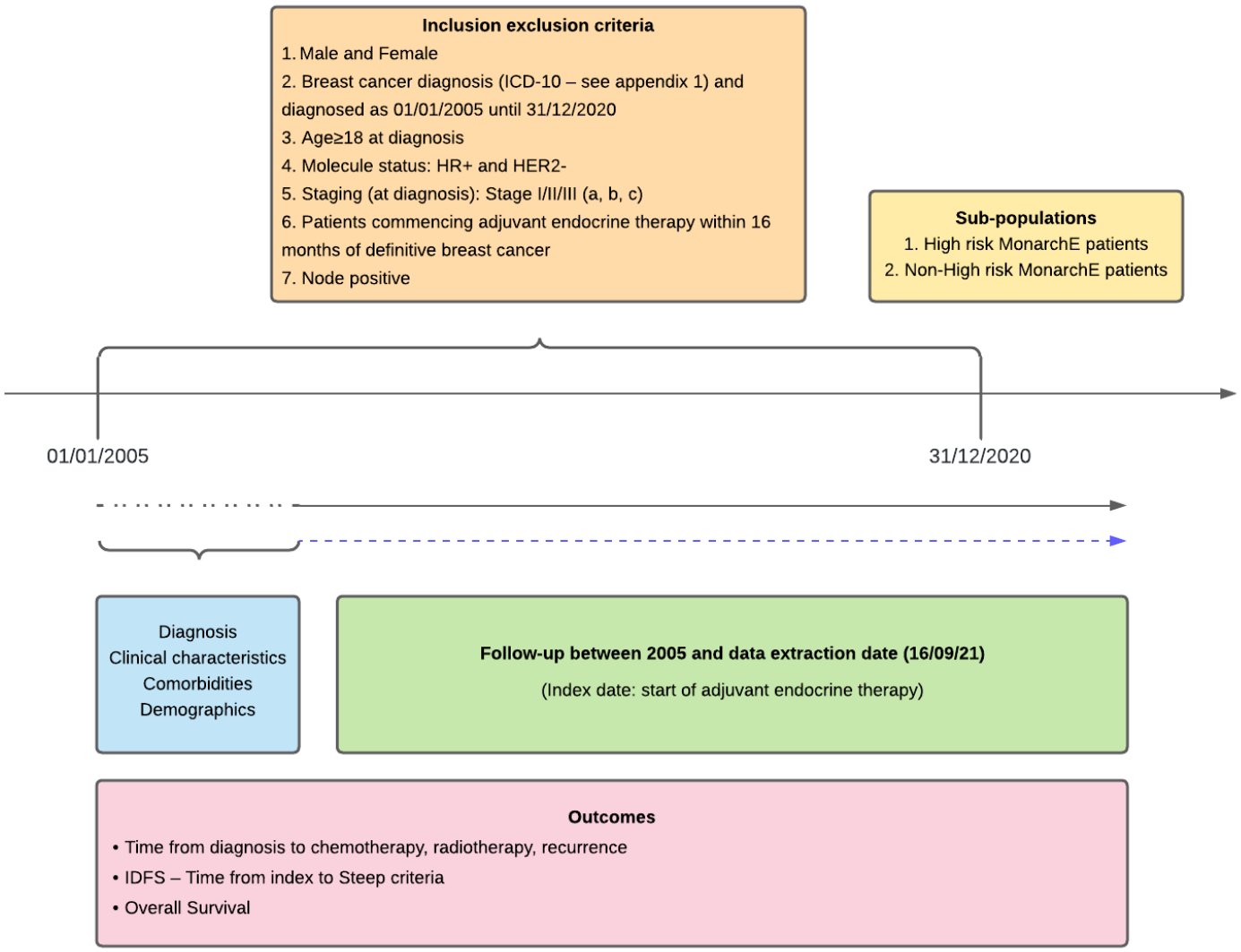


Figure 1: Timeline

Definition of Invasive Disease Free Survival Endpoint per STEEP criteria (11):

- Ipsilateral invasive breast tumour recurrence (IIBTR): invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- Second primary non-breast invasive cancer.

5.3 Subjects

The selection criteria were the following:

- Male and Female with breast cancer diagnosis (ICD-10 - see Appendix 1) and diagnosed as of 1st of January 2005 until 31st of December 2020
- Age ≥ 18 at diagnosis
- Molecular status: HR+ and HER2-
- Staging (at diagnosis): Stage I/II/III (a,b,c)
- Patients commencing adjuvant endocrine therapy within 16 months of definitive breast cancer surgery
- Node positive

Patients meeting the following criteria were excluded from the study:

- Initial diagnosis of breast cancer was metastatic (stage IV)
- Treated with Abemaciclib within the monarchE clinical trial

This study were performed on several populations, as shown in figure 2.

5.3.1 All Patients

As described in section 6.3.

5.3.2 MonarchE eligible Patients (High Risk)

High-risk patients for disease recurrence as per monarchE trial will then be identified according to their histopathological parameters including: Stage IB-Stage IIIC, pathological tumour involvement in ≥ 4 ipsilateral axillary lymph nodes, or, pathological tumour involvement in 1-3 ipsilateral axillary lymph node(s) and meet at least high histologic/nuclear Grade 3 as defined by the modified Bloom-Richardson grading system also known as the Nottingham scale (12, 13), pathological primary tumour size ≥ 5 cm. Microscopic and macroscopic tumor involvement are allowed; ipsilateral internal mammary and supraclavicular lymph nodes are allowed, but will not count toward the number of positive lymph nodes.

Of those, the sub population of interest within this study (aligned to inclusion criteria for the majority of patients (~91% in the monarchE trial) has the following criteria:

- HR receptor positive, HER2 negative
- Meeting one of the following criteria:
    - Patients with ≥ 4 ipsilateral axillary LN on pathological staging OR
    - Pathological tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) (for patients who received neoadjuvant therapy also cytological tumor involvement at time of initial diagnosis is allowed) and meet at least one of the following criteria:
        - Grade 3 as defined by a combined score of at least 8 points per the modified Bloom-Richardson grading system (Elston and Ellis 1991), also known as the Nottingham scale.
        - Pathological primary invasive tumor size ≥ 5cm (for patients who received neoadjuvant therapy primary tumor size ≥5 cm on breast imaging is allowed).

5.3.3 Non-MonarchE eligible Patients (non-high risk)

This includes HR+/HER2- patients, not meeting monarchE inclusion criteria.

5.3.4 Summary

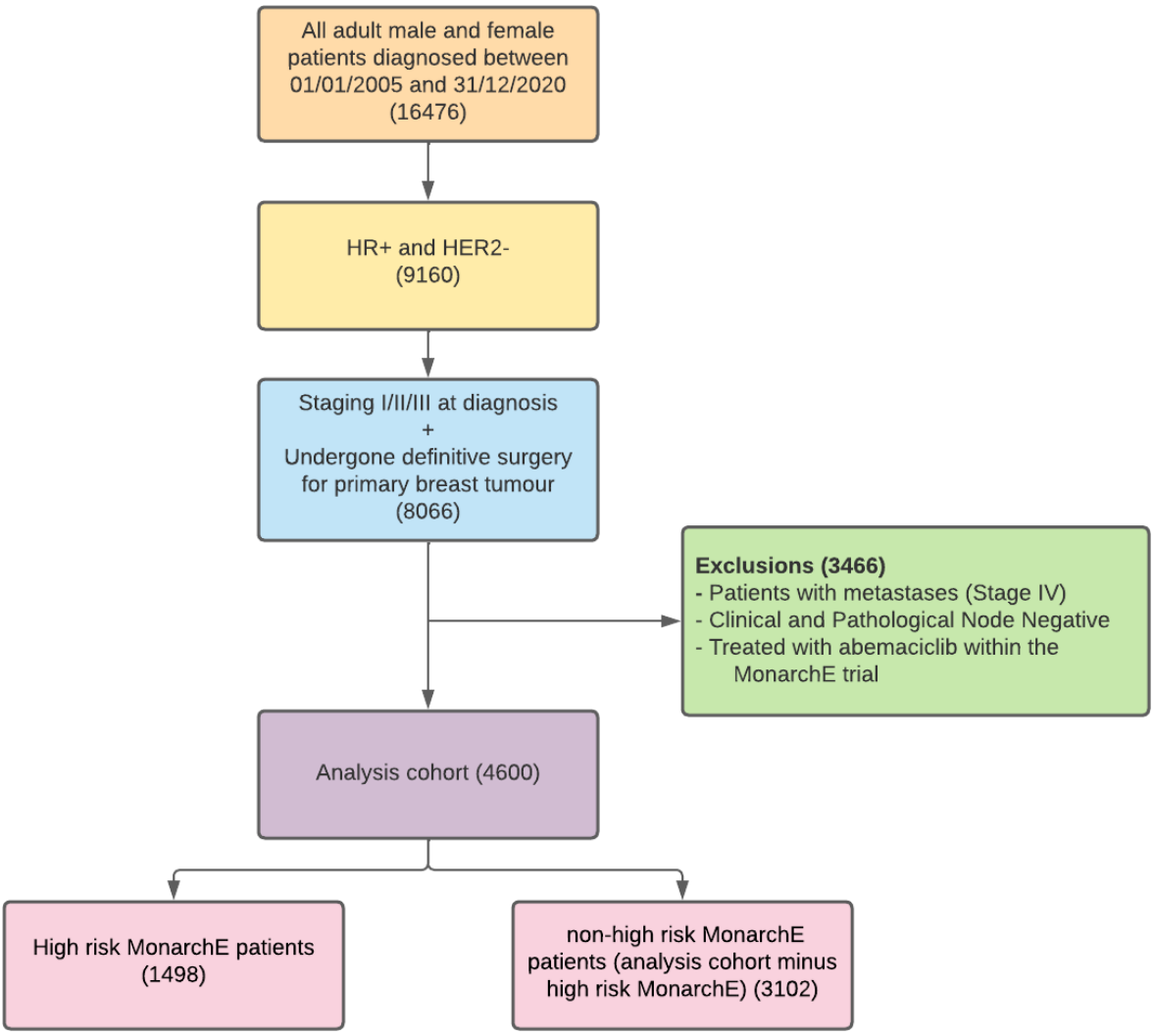


Figure 2: Subsets and population selection process

5.4 Variables and data sources

The variables analysed can be found in the below table:

Table 1: Variables and operational definitions

Data item	Format	Data Field	Source	Notes
Study ID	char	S_ID		
MonarchE Eligible HighRisk Flag	binary	mon_HR	According to criteria	
Demographics				
Age at diagnosis	integer	diag_age	SMR06/QPI	
Year of Diagnosis	integer	diag_year	SMR06/QPI	
Sex	char	sex	SMR06/QPI	
SIMD quintile	integer	simd_q	Derived from postcode, QPI	
Residential Area	char	res_area	Derived from postcode,QPI	Urban, Rural (binary)
Patient in Clinical Trial	binary	c_trial	QPI	
ECOG/Performance status	integer	perform	Chemocare	From 2016
Height	numeric	height	Chemocare	
Weight	numeric	weight	Chemocare	
Surface Area	numeric	s_area	Chemocare	
Diagnosis and Pathological Details				
Mode of Presentation	binary	screening	QPI	Screening, Symptomatic
Menopausal Status	binary	m_status	QPI/derived	Derived from age at diagnosis and Goserelin prescription
Laterality	char	side	SMR06/QPI	
Clinical T Stage	integer	cT	SMR06/QPI	
Clinical N Stage	integer	cN	SMR06/QPI	
Pathological T Stage	integer	pT	SMR06	
Pathological N Stage	integer	pN	SMR06	
Inflammatory Breast Cancer	binary	inflam	SMR06/QPI	
AJCC Staging	char	ajcc_stage	SMR06/QPI	
Oestrogen Receptor Status	binary	er_status	SMR06/QPI	
Progesterone Receptor Status	binary	pr_status	QPI	
Tumour Size	numeric	size	QPI	in mm
Tumour Grade	integer	grade	SMR06/QPI	
Genomic Testing				
Oncotype DX	binary	otdx	QPI	
Oncotype DX score	integer	otdx_score	QPI	

Surgery				
Mastectomy	binary	mastectomy	QPI/SESCD	
Wide Local Excision	binary	wle	QPI/SESCD	
Axillary Node Clearance	binary	anc	QPI/SESCD	
Sentinel Lymph Node Biopsy	binary	slnb	QPI/SESCD	
Systemic Therapy and Treatment				
Adjuvant Tamoxifen	binary	tamoxifen	PIS	First adjuvant endocrine therapy
Adjuvant Letrozole	binary	letrozole	PIS	First adjuvant endocrine therapy
Adjuvant Anastrozole	binary	anastrozole	PIS	First adjuvant endocrine therapy
Adjuvant Exemestane	binary	exemestane	PIS	First adjuvant endocrine therapy
Adjuvant Goserelin	binary	goserelin	PIS	
Received Neoadjuvant Chemotherapy	binary	nact	QPI/SESCD/ChemoCare	
Received Adjuvant Chemotherapy	binary	act	QPI/SESCD/ChemoCare	
Neoadjuvant Taxane-based Chemotherapy	binary	n_anthra_CT	ChemoCare/SESCD	
Neoadjuvant Anthracycline-based Chemotherapy	binary	n_taxa_CT	ChemoCare/SESCD	
Neoadjuvant Other Chemotherapy	binary	n_other_CT	ChemoCare/SESCD	
Adjuvant Anthracycline-based Chemotherapy	binary	anthra_CT	ChemoCare/SESCD	
Adjuvant Taxane-based Chemotherapy	binary	taxa_CT	ChemoCare/SESCD	
Adjuvant Other Chemotherapy	binary	other_CT	ChemoCare/SESCD	
Received Radiotherapy	binary	radio	QPI/SMR06	
Timelines				
Time from Diagnosis to First Chemotherapy	integer	t_diag_ct	SMR06/QPI	in days
Time from Diagnosis to Primary Surgery	integer	t_diag_surg	SMR06/QPI	in days
Time from Diagnosis to Radiotherapy	integer	t_diag_rad	SMR06/QPI	in days
Time from Diagnosis to IDFS event	integer	t_idfs	QPI/SESCD	in days
Time from Start of adjuvant Endocrine Therapy to IDFS event	integer	t_et_idfs	QPI/SESCD	in days
Time from Primary Surgery to IDFS event	integer	t_surg_idfs	QPI/SESCD	in days
Time from Diagnosis to Death	integer	t_os	SMR06/QPI/GRO	in days
Time from Start of adjuvant Endocrine Therapy to Death	integer	t_et_idfs	SMR06/QPI/GRO	in days
Time from Diagnosis to last Follow-up	integer	t_fu	SMR06/QPI/GRO	in days
Time from Diagnosis to the first recurrence event (any)	integer	t_recur	QPI/SESCD	in days

Data item	Format	Data Field	Source	Notes
Outcomes and Follow-Up				
Recurrence (any)	binary	recur	QPI/SESCD	
Death	binary	death	GRO/QPI	
Invasive Disease-free Event	binary	idfs_e	QPI/SESCD/GRO	
Local Recurrence	binary	local_recur	QPI/SESCD	
Distant Recurrence	binary	dist_recur	QPI/SESCD	
Comorbidity and Healthcare Resource Utilisation				
Charlson Comorbidity Index*	integer	cci	SMR01	
Number of Inpatient Visits after Diagnosis	integer	n_inp	SMR01	
Number of Outpatient Visits after Diagnosis	integer	n_outp	SMR01	
Average Length of Stay for Inpatient Visits	numeric	a_los	SMR01	in days
Total Length of Stay	numeric	t_los	SMR01	in days

(*)The Charlson comorbidity index includes the following:

- Myocardial infarction
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Dementia
- Chronic pulmonary disease
- Rheumatic disease
- Peptic ulcer disease
- Mild liver disease
- Diabetes without chronic complication
- Diabetes with chronic complication
- Hemiplegia or paraplegia
- Renal disease
- Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin
- Moderate or severe liver disease
- Metastatic solid tumour
- AIDS/HIV

5.5 Bias

As the study objectives are descriptive in nature, statistical adjustments for bias and confounding will not be made.

5.6 Study size

All patients with a diagnosis of breast cancer between 01/01/2005 and 31/12/2020 (calendar year), were included in the study. Due to the observational nature of this study, and since no hypothesis testing was done, formal calculation of sample size and statistical power are not included. The estimated number of cases corresponding to the above critera (section 6.3) in the NHS Lothian region includes 4600 cases.

The sizes of the sub-populations are:

- High risk monarchE Cohort: 1498
  - Patients with ≥ 4 ipsilateral axillary LN on pathological staging (criteria 1): 777
  - Pathological tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) and Grade 3 (criteria 2a): 201
  - Pathological tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) and pathological primary invasive tumor size ≥ 5cm (criteria 2b): 520
- Non high risk monarchE cohort: 3102

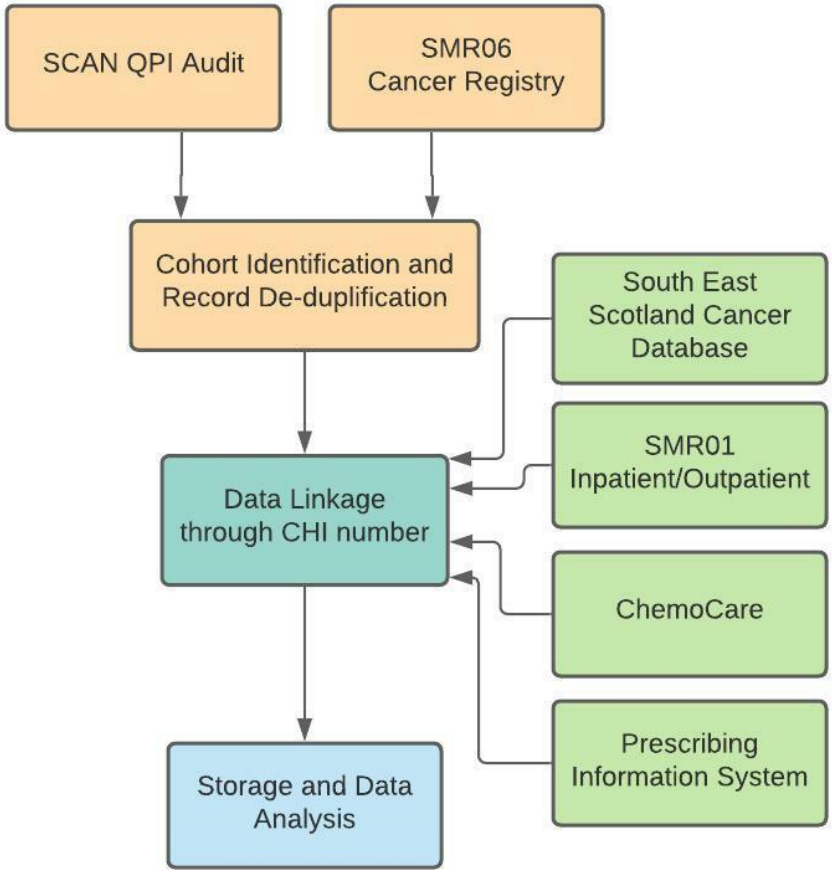
5.7 Data transformation

Using the SMR06 Cancer Registry and SCAN QPI Audit as the primary sources, the index case for each patient was selected as the earliest HR+ Breast Cancer diagnosis since 01/01/2005, and according to the specified selection criteria. If the patient record presented multiple simultaneous diagnoses, duplicates were excluded by selecting the diagnosis record with the highest risk factors (i.e. higher grade, higher size and nodal stages). Index cases were then linked using the patients' CHI number to other data sources for treatment information and follow-up. These sources include: SMR01 Acute Episodes, ChemoCare, SESCD, and PIS.

5.8 Disclosure

All data analysis was performed by NHS analysts in accordance with data governance requirements. Censoring for purposes of disclosure control was undertaken as per NHS Lothian disclosure control policy, including the suppression of numbers less than 10. Small numbers are included in section 7.4 as the analysis represents Kaplan-Meier estimates rather than actual patient numbers and is considered non-disclosive.

Figure 3: Data sources



5.9 Statistical methods

5.9.1 Main summary measures

All analyses performed were purely descriptive and no formal or statistical comparisons were made. The descriptive statistics that were reported depending on the type of variable being described: numeric variables were summarized by their mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum and number of non-missing observations. Categorical variables were summarized by the total number of non-missing observations and the number and proportion of observations in each category. Time to event data were presented using Kaplan Meier curves, censored at last follow-up timepoint. Outcomes were measured as proportion of patients who have not reached the survival outcome at year one, two, three, four, five, and ten, including 95% confidence intervals. Number at risk (n.risk) and number of events (n.events) are provided as well for the sub-analysis.

5.9.2 Main statistical methods

See 6.9.1

5.9.3 Missing values

Missing values were expected. No imputations were made for missing data. Proportion of non-missing observations were reported as applicable.

5.9.4 Sensitivity analyses

N/A

5.9.5 Amendments to the statistical analysis plan

N/A

5.10 Quality Control

The accuracy of recurrence events used as IDFS end point in this project underwent quality control against a sample of patients with and without recurrence for each of the database sources used (figure 4).

The three data sources that provided IDFS information were SESCD, SCAN QPI and the Metastatic Breast Cancer List (this is a list of patients maintained by the Secondary Breast Cancer Specialist Nursing Service in NHS Lothian). The number of events from each source were QPI (83%), SESCD (11%) and Met BC list (6%).

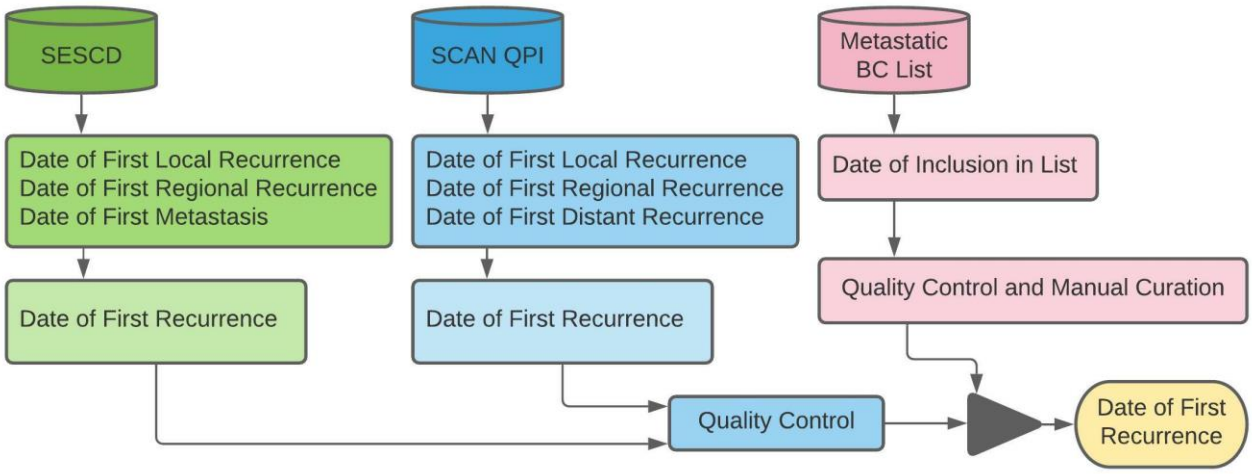
Due to the use of several sources and the accuracy of the data, hierarchy was implemented where the newly identified contralateral breast cancer, secondary breast cancer and new primary cancers were prioritized from SCAN QPI, followed by SESCD, and metastatic BC list (figure 4).

17 patients registered as M0 in the cancer registry (SMR06) were, with retrospect, found to have metastatic disease at diagnosis and were excluded from the analysis. The 51 recurrence events initially sourced through the metastatic breast cancer list were all manually checked through the quality control process, and 23 inaccurate events were excluded or replaced with alternative events either because they are metastatic at diagnosis (17), or because there were identified with alternative dates in SCAN QPI or SESCD (4), or otherwise found to be ineligible and excluded (1) or occurred after data-cut (1). The included 29 events are 100% accurate within +/- 6 weeks and represent 6% of the total sourced recurrence events.

The outcomes are as follows:

	SESCD	**SCAN QPI**
Patients with recurrence		
Accuracy (+/- 6 weeks)	96%	92%
% of sourced recurrence events	11%	83%
Patients without recurrence		
Accuracy (no recurrence)	100%	100%

Figure 4: Disease Recurrence Selection Process



6. Results

6.1 Descriptive data

Table 2: Patients characteristics

Cohorts	All		High Risk MonarchE		Non-High Risk MonarchE	
Patient count						
	N	%	N	%	N	%
N	4600	100	1498	32.6	3102	67.4
Sex						
	N	%	N	%	N	%
Female	4569	99.3	1485	99.1	3084	99.4
Male	31	0.7	13	0.9	18	0.6
Age at Diagnosis						
	Median	Range	Median	Range	Median	Range
	63	23 – 102	59	24 – 93	66	23 – 102
Age Group						
	N	%	N	%	N	%
<40	156	3.4	84	5.6	72	2.3
40-44	251	5.5	103	6.9	148	4.8
45-49	446	9.7	192	12.8	254	8.2
50-54	597	13	234	15.6	363	11.7
55-59	479	10.4	161	10.7	318	10.3
60-64	465	10.1	160	10.7	305	9.8
65-69	516	11.2	165	11	351	11.3
70-74	445	9.7	156	10.4	289	9.3
75+	1245	27.1	243	16.2	1002	32.3
Menopausal Status						
	N	%	N	%	N	%
Pre	912	19.8	410	27.4	502	16.2
Peri	76	1.7	17	1.1	59	1.9
Post	3612	78.5	1071	71.5	2541	81.9
Clinical Trial Involvement						
	N	%	N	%	N	%
No	2962	64.4	866	57.8	2096	67.6
Yes	126	2.7	74	4.9	52	1.7
NA	1512	32.9	558	37.2	954	30.8
Follow-up (N = 4600 | 1498 | 3102)						
	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD
Duration (in years)	6.86 (6.03)	4.57	6.8 (6.01)	4.3	6.88 (6.05)	4.7

Cohorts	All		High Risk MonarchE		Non-High Risk MonarchE	
Body Index (N= 507 | 312 | 195)						
	Mean	SD	Mean	SD	Mean	SD
Height (m)	1.63	0.07	1.62	0.07	1.63	0.06
Weight (kg)	76.98	17.23	77.87	16.8	75.55	17.84
Surface Area (m^2)	1.82	0.19	1.82	0.19	1.81	0.19
Urban - Rural Indicator						
	N	%	N	%	N	%
Rest of Scotland	3871	84.2	1222	81.6	2649	85.4
Rural Scotland	729	15.8	276	18.4	453	14.6

Table 3: Diagnosis and surgery characteristics

Cohorts	All		High Risk MonarchE		Non-High Risk MonarchE	
Patient count						
	N	%	N	%	N	%
N	4600	100	1498	32.6	3102	67.4
Pathological Tumour Size (in population not given neoadjuvant chemotherapy) (N=3781 | 1125 | 2656)						
	N	%	N	%	N	%
<20mm	1268	33.5	257	22.8	1011	38.1
20-50mm	1197	31.7	539	47.9	658	24.8
>50mm	347	9.2	310	27.6	37	1.4
Missing	969	25.6	19	1.7	950	35.8
Pathological number of nodes involved (in population not given neoadjuvant chemotherapy) (N=3781 | 1125 | 2656)						
	N	%	N	%	N	%
0	326	8.6	0	0	326	12.3
1-3	1708	45.2	539	47.9	1169	44
4-9	393	10.4	393	34.9	0	0
10+	193	5.1	193	17.2	0	0
Missing	1161	30.7	0	0	1161	43.7
AJCC stage (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
1	1386	30.1	214	14.3	1172	37.8
2	2276	49.5	933	62.3	1343	43.3
3A	188	4.1	126	8.4	62	2
3B	416	9	164	10.9	252	8.1
3C	30	0.7	15	1	15	0.5
X	304	6.6	46	3.1	258	8.3

Cohorts	All		High Risk MonarchE		Non-High Risk MonarchE	
Clinical T Stage (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
0	<10	<0.2	<10	<0.7	<10	<0.3
1	1731	37.6	390	26.0	1341	43.2
2	1851	40.2	716	47.8	1135	36.6
3	288	6.3	178	11.9	110	3.5
4	422	9.2	166	11.1	256	8.3
X	>298	>6.5	>38	>2.5	>250	>8.1
Clinical N Stage (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
1	1422	30.9	764	51	658	21.2
2+	94	2	45	3	49	1.6
X	557	12.1	108	7.2	449	14.5
NA	2527	54.9	581	38.8	1946	62.7
Tumour Grade (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
1	552	12	36	2.4	516	16.6
2	2779	60.4	592	39.5	2187	70.5
3	>1201	>26.1	>860	>57.4	341	11
Unknown	<68	<1.5	<10	<0.7	58	1.9
ER Status (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
Negative	<10	<0.2	<10	<0.7	<10	<0.3
Positive	>4590	>99.8	>1488	>99.3	3092	>99.7
PR Status (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
Negative	3054	66.4	949	63.4	2105	67.9
Positive	1546	33.6	549	36.6	997	32.1
OncotypeDX Score (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
<25	10	0.2	<10	0.7	<10	<0.3
≥25	<10	<0.2	<10	0.7	0	0
No Test	>4580	>99.6	>1480	>98.6	>3092	>99.7
Charlson Comorbidity Index (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
0	2957	64.3	1056	70.5	1901	41.3
1	187	4.1	33	2.2	154	3.3
2	<70	<1.5	<10	<0.7	60	1.3
3+	<62	<1.3	<10	<0.7	52	1.1
NA	>1324	>28.8	>389	>26	935	20.3

Table 4: Treatment descriptions

Cohorts	All		High Risk MonarchE		Non-High Risk MonarchE	
Patient count						
	N	%	N	%	N	%
N	4600	100	1498	32.6	3102	67.4
Chemotherapy (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
Neo-adjuvant only	264	5.7	123	8.2	141	4.6
Adjuvant only	990	21.5	654	43.7	336	18.8
Both neoadjuvant and adjuvant	555	12.1	250	16.7	305	9.8
NA	2791	60.7	471	31.4	2320	74.8
Chemotherapy: Taxane only (N= 260 | 165 | 95)*						
	N	%	N	%	N	%
Neo-adjuvant	39	4.8	27	7.2	12	2.7
Adjuvant	230	14.9	144	15.9	86	13.4
Chemotherapy: Anthracycline only (N= 422 | 186 | 236)*						
	N	%	N	%	N	%
Neo-adjuvant	109	13.3	52	13.9	57	12.8
Adjuvant	326	21.1	142	15.7	184	28.7
Chemotherapy: Anthracycline and Taxane (N= 866 | 618 | 248)*						
	N	%	N	%	N	%
Neo-adjuvant	263	32.1	145	38.9	118	26.5
Adjuvant	644	41.7	506	55.9	138	21.5
Chemotherapy: Other (Non-anthracycline non-taxane) (N= 419 | 157 | 262)*						
	N	%	N	%	N	%
Neo-adjuvant	408	49.8	149	39.9	259	58.1
Adjuvant	345	22.3	112	12.4	233	36.4
Adjuvant Endocrine Therapy (all) (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
Anastrozole	225	4.9	99	6.6	126	4.1
Exemestane	<20	<0.4	<10	<0.7	<10	<0.3
Letrozole	1888	41	516	34.4	1372	44.2
Tamoxifen	864	18.8	273	18.2	591	19.1
Unspecified	>1603	34.9	>600	>40	>1003	32.3
Ovarian Function Suppression (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
Goserelin	219	4.8	124	8.3	95	3.1
NA	4381	95.2	1374	91.7	3007	96.9

(*)Denominator for each chemotherapy is calculated as the sum of neo-adjuvant only and both neoadjuvant and adjuvant, or adjuvant only and both neoadjuvant and adjuvant for each respective risk group

Cohorts	All	High Risk MonarchE	Non-High Risk MonarchE

Adjuvant Endocrine Therapy (Premenopausal only) (N= 998 | 427 | 571)						
	N	%	N	%	N	%
Anastrozole	34	3.4	19	4.4	15	2.7
Exemestane	<10	<1.0	<10	<2.5	0	0
Letrozole	102	10.3	51	11.9	51	9.1
Tamoxifen	520	52.6	214	50.1	306	54.5
NA	>331	>33.2	>143	>33.4	189	33.7
Adjuvant Endocrine Therapy (Postmenopausal only) (N= 3612 | 1071 | 2541)						
	N	%	N	%	N	%
Anastrozole	191	5.3	80	7.5	111	4.4
Exemestane	<10	<0.3	0	0	<10	<0.3
Letrozole	1786	49.4	465	43.4	1321	52
Tamoxifen	344	9.5	59	5.5	285	11.2
NA	>1281	>35.4	467	43.6	>814	>32.1
Radiotherapy (N= 4600 | 1498 | 3102)						
	N	%	N	%	N	%
Received	3343	72.7	1380	92.1	1963	63.3
NA	1257	27.3	118	7.9	1139	46.7

Table 5: Timelines

Cohorts	**All patients**		**High risk MonarchE patients**		**Non high risk MonarchE patients**	
Time from Diagnosis to First Chemotherapy (N= 1809 | 1027 | 782)						
	Mean	SD	Mean	SD	Mean	SD
Time (days)	78.61	66.03	80.88	64.24	75.9	68.05
Time from Diagnosis to Surgery (N = 4600 | 1498 | 3102)						
	Mean	SD	Mean	SD	Mean	SD
Time (days)	76.09	155.67	87.69	171.9	71.2	148.08
Time from Diagnosis to Radiotherapy (N = 3343 | 1380 | 1963)						
	Mean	SD	Mean	SD	Mean	SD
Time (days)	162.48	98.22	214.95	89.88	137.95	92.17

Table 6: Health care resource utilisation and timelines

Cohorts	All		High Risk MonarchE		Non-High Risk MonarchE	
Count of Inpatient Visits after Diagnosis (first two years from diagnosis) (N = 3250 | 1093 | 2157)						
	Median (Mean)	SD	Median (Mean)	SD	Median (Mean)	SD
Inpatient admissions	1 (2)	2.20	2 (2.3)	2.17	1 (1.9)	2.21
Count of Outpatient Visits after Diagnosis (first two years from diagnosis) (N = 3250 | 1093 | 2157)						
	Median (Mean)	SD	Median (Mean)	SD	Median (Mean)	SD
Outpatient visits	1 (4.5)	6.14	7 (7.1)	7.20	1 (3.2)	5.06
Length of Stay for Inpatient Admissions (first two years from diagnosis) (N = 3250 | 1093 | 2157)						
	Mean	SD	Mean	SD	Mean	SD
Average (days)	6.6	13.08	4.9	8.45	7.5	15.01
Total Length of Stay (first two years from diagnosis) (N = 3250 | 1093 | 2157)						
	Mean	SD	Mean	SD	Mean	SD
Average (days)	13.7	30.58	10.8	18.34	15.1	– 35.10
Time from Diagnosis to Recurrence (N = 381 | 196 | 185)						
	Median	SD	Median	SD	Median	SD
Time (months)	39.1	33.72	33.9	29.77	46.6	36.57
Time from start of adjuvant endocrine therapy to IDFS event (N = 1684 | 489 | 1195)						
	Median	SD	Median	SD	Median	SD
Time (months)	42.1	41.04	44.8	40.33	41.3	41.32
Time from Start of adjuvant endocrine therapy to death (N = 1520 | 435 | 1085)						
	Median	SD	Median	SD	Median	SD
Time (months)	46.3	42.02	52.5	40.19	42.9	42.59
Time from Primary Surgery to IDFS event (N = 1684 | 489 | 1195)						
	Median	SD	Median	SD	Median	SD
Time (months)	51.7	43.78	45.1	41.27	60.3	45.02
Time from Diagnosis to Death (N = 1520 | 435 | 1085)						
	Median	SD	Median	SD	Median	SD
Time (months)	49.3	42.57	56.1	40.46	44.5	43.14

6.2 Outcomes

Table 7: IDFS results

All patients						
Years	n.risk	n.event	surv	std.err	lower	upper
1	4278	209	0.95	0.00	0.95	0.96
2	3735	274	0.89	0.00	0.88	0.90
3	3258	221	0.84	0.01	0.83	0.85
4	2848	198	0.78	0.01	0.77	0.80
5	2478	184	0.73	0.01	0.72	0.75
10	1109	452	0.56	0.01	0.55	0.58
High risk MonarchE patients						
Years	n.risk	n.event	surv	std.err	lower	upper
1	1426	31	0.98	0.00	0.97	0.99
2	1248	84	0.92	0.01	0.91	0.93
3	1075	70	0.87	0.01	0.85	0.88
4	940	55	0.82	0.01	0.80	0.84
5	804	62	0.76	0.01	0.74	0.79
10	333	143	0.59	0.02	0.56	0.62
Non high risk MonarchE patients						
Years	n.risk	n.event	surv	std.err	lower	upper
1	2852	178	0.94	0.00	0.93	0.95
2	2487	190	0.88	0.01	0.87	0.89
3	2183	151	0.82	0.01	0.81	0.84
4	1908	143	0.77	0.01	0.75	0.78
5	1674	122	0.72	0.01	0.70	0.73
10	776	309	0.55	0.01	0.53	0.57

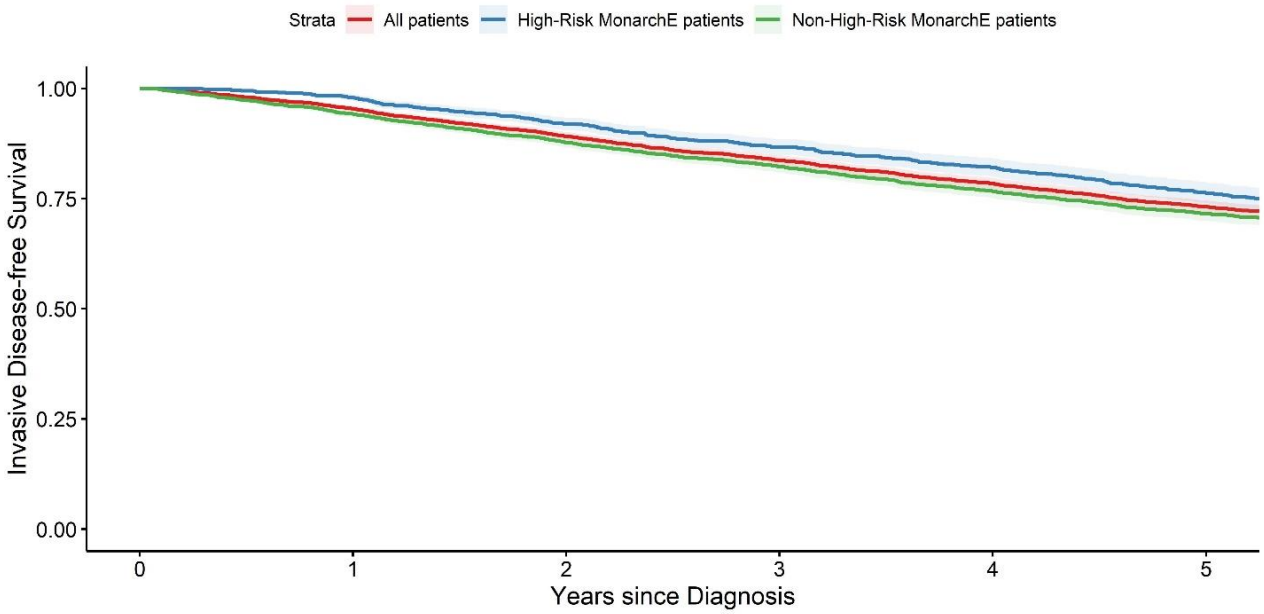


Figure 5: Invasive Disease Free Survival

Table 8: OS results

All patients						
Years	n.risk	n.event	surv	std.err	lower	upper
1	4316	171	0.96	0.00	0.96	0.97
2	3837	209	0.91	0.00	0.91	0.92
3	3377	198	0.87	0.01	0.86	0.88
4	2990	171	0.82	0.01	0.81	0.83
5	2629	168	0.77	0.01	0.76	0.79
10	1219	446	0.61	0.01	0.59	0.63
High risk MonarchE patients						
Years	n.risk	n.event	surv	std.err	lower	upper
1	1441	16	0.99	0.00	0.98	0.99
2	1295	51	0.95	0.01	0.94	0.96
3	1133	57	0.91	0.01	0.89	0.92
4	997	54	0.86	0.01	0.85	0.88
5	860	61	0.81	0.01	0.79	0.83
10	365	147	0.63	0.02	0.60	0.67
Non high risk MonarchE patients						
Years	n.risk	n.event	surv	std.err	lower	upper
1	2875	155	0.95	0.00	0.94	0.96
2	2542	158	0.90	0.01	0.88	0.91
3	2244	141	0.84	0.01	0.83	0.86
4	1993	117	0.80	0.01	0.78	0.81
5	1769	107	0.75	0.01	0.74	0.77
10	854	299	0.60	0.01	0.58	0.62

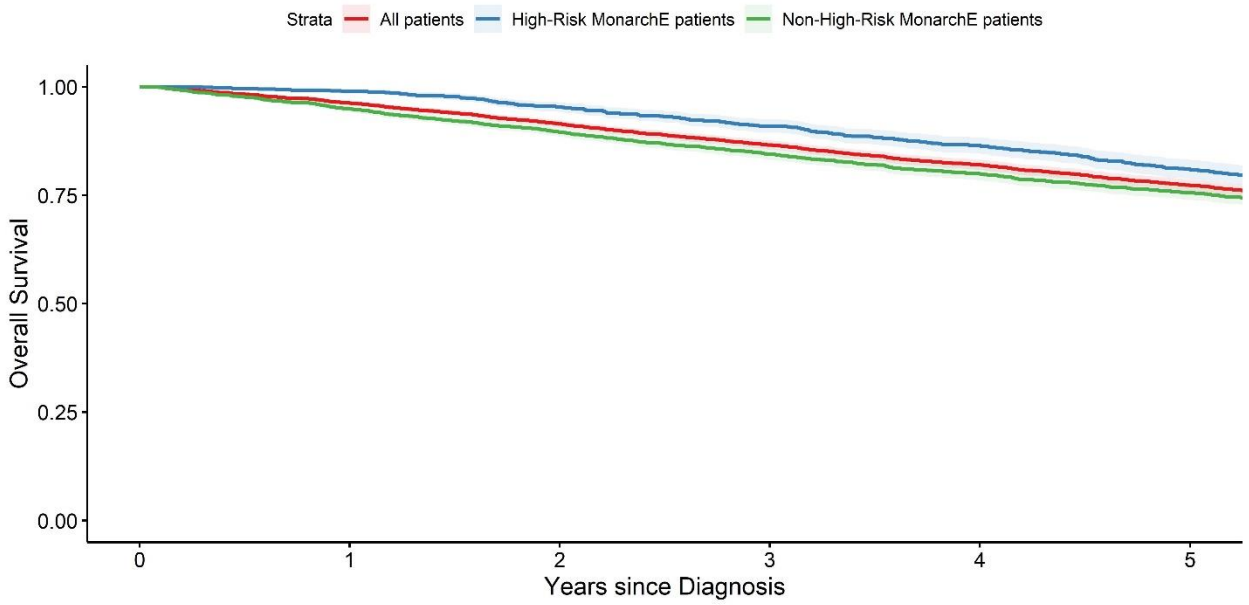


Figure 6: Overall Survival

6.3 Other analyses

6.3.1 Subgroup Analyses

Outcomes were presented by subgroups of interest, including:

- Comorbidity level
- Postmeopausal status
- Number of positive lymph nodes
- Tumour size
- PR-
- Grade
- Age group
- Inflammatory
- Pre-post COVID pandemic (01/01/2020 cut-off date)

6.3.1.1 IDFS results

Figure 7: IDFS by Charlson Comorbidity Index

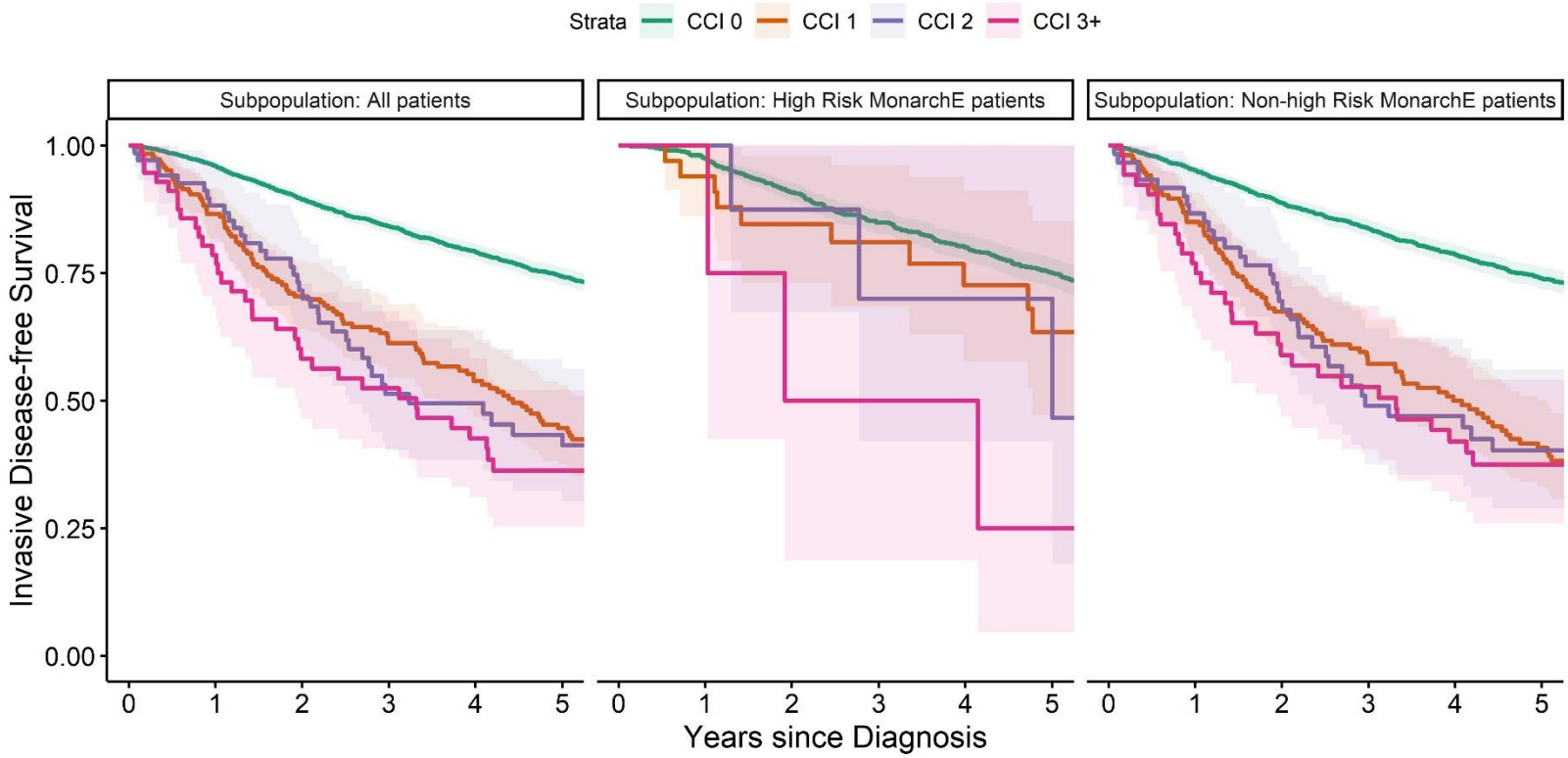


Table 9: IDFS by comorbidity level

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
strata	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
0	1	2768	117	0.96	0.00	0.95	0.97	998	26	0.97	0.00	0.97	0.98	1770	91	0.95	0.00	0.94	0.96
	2	2429	184	0.89	0.01	0.88	0.91	880	67	0.91	0.01	0.89	0.93	1549	117	0.89	0.01	0.87	0.90
	3	2126	138	0.84	0.01	0.83	0.86	756	55	0.85	0.01	0.83	0.87	1370	83	0.84	0.01	0.82	0.85
	4	1856	123	0.79	0.01	0.78	0.81	658	42	0.80	0.01	0.78	0.83	1198	81	0.79	0.01	0.77	0.81
	5	1619	108	0.74	0.01	0.73	0.76	563	39	0.75	0.01	0.72	0.78	1056	69	0.74	0.01	0.72	0.76
	10	738	278	0.58	0.01	0.56	0.61	223	106	0.57	0.02	0.53	0.61	515	172	0.59	0.01	0.56	0.62
1	1	160	25	0.87	0.02	0.82	0.92	31	2	0.94	0.04	0.86	1.00	129	23	0.85	0.03	0.80	0.91
	2	122	29	0.70	0.03	0.64	0.77	25	3	0.85	0.06	0.73	0.98	97	26	0.67	0.04	0.60	0.75
	3	96	15	0.61	0.04	0.55	0.69	21	1	0.81	0.07	0.69	0.96	75	14	0.57	0.04	0.50	0.66
	4	77	11	0.54	0.04	0.47	0.62	17	2	0.73	0.08	0.58	0.91	60	9	0.50	0.04	0.42	0.59
	5	62	13	0.45	0.04	0.37	0.53	14	2	0.63	0.10	0.47	0.85	48	11	0.41	0.04	0.33	0.50
	10	16	26	0.21	0.04	0.15	0.30	<10	1	0.59	0.10	0.42	0.82	<10	25	0.13	0.04	0.08	0.23
2	1	60	8	0.88	0.04	0.81	0.96	<10	0	1.00	0.00	1.00	1.00	52	8	0.87	0.04	0.78	0.96
	2	46	11	0.72	0.06	0.62	0.83	<10	1	0.88	0.12	0.67	1.00	40	10	0.70	0.06	0.59	0.82
	3	29	12	0.51	0.06	0.40	0.65	<10	1	0.70	0.18	0.42	1.00	25	11	0.49	0.07	0.37	0.64
	4	25	1	0.49	0.06	0.38	0.64	<10	0	0.70	0.18	0.42	1.00	22	1	0.47	0.07	0.35	0.62
	5	21	3	0.43	0.07	0.32	0.58	<10	0	0.70	0.18	0.42	1.00	18	3	0.40	0.07	0.29	0.56
	10	<10	11	0.14	0.06	0.06	0.33							<10	10	0.12	0.06	0.05	0.31
3+	1	44	12	0.79	0.05	0.69	0.90	<10	0	1.00	0.00	1.00	1.00	40	12	0.77	0.06	0.66	0.89
	2	30	11	0.58	0.07	0.47	0.73	<10	2	0.50	0.25	0.19	1.00	28	9	0.59	0.07	0.47	0.74
	3	27	3	0.52	0.07	0.41	0.68	<10	0	0.50	0.25	0.19	1.00	25	3	0.53	0.07	0.40	0.68
	4	21	5	0.43	0.07	0.31	0.58	<10	0	0.50	0.25	0.19	1.00	19	5	0.42	0.07	0.30	0.58
	5	13	3	0.36	0.07	0.25	0.52	<10	1	0.25	0.22	0.05	1.00	12	2	0.37	0.07	0.26	0.54
	10	<10	9	0.10	0.05	0.04	0.27	<10	0	0.25	0.22	0.05	1.00	<10	<10	0.08	0.05	0.02	0.27

Figure 8: IDFS by Menopausal Status

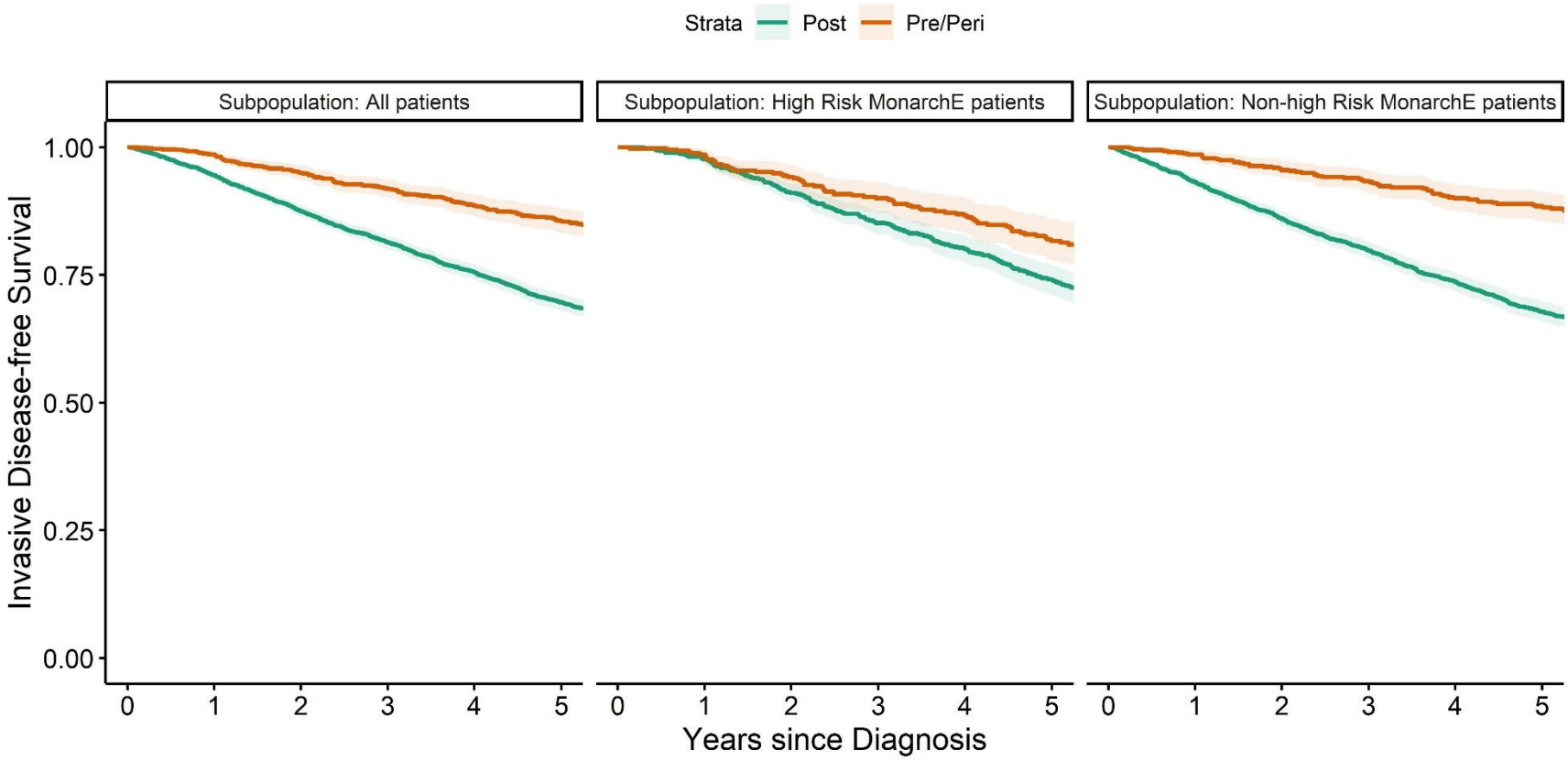


Table 10: IDFS by menopausal status

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
mstatus	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Pre/Peri	1	954	14	0.99	0.00	0.98	0.99	411	6	0.99	0.00	0.98	1.00	543	8	0.99	0.01	0.98	1.00
	2	866	34	0.95	0.01	0.94	0.96	371	18	0.94	0.01	0.92	0.97	495	16	0.96	0.01	0.93	0.97
	3	781	27	0.92	0.01	0.90	0.94	325	16	0.90	0.02	0.87	0.93	456	11	0.93	0.01	0.91	0.96
	4	709	28	0.89	0.01	0.86	0.91	294	12	0.87	0.02	0.83	0.90	415	16	0.90	0.01	0.87	0.93
	5	636	23	0.86	0.01	0.83	0.88	251	16	0.82	0.02	0.78	0.86	385	7	0.88	0.02	0.85	0.91
	10	350	78	0.73	0.02	0.69	0.76	121	35	0.68	0.03	0.62	0.73	229	43	0.77	0.02	0.71	0.80
Post	1	3324	195	0.95	0.00	0.94	0.95	1015	25	0.98	0.00	0.97	0.99	2309	170	0.93	0.01	0.92	0.94
	2	2869	240	0.87	0.01	0.86	0.89	877	66	0.91	0.01	0.89	0.93	1992	174	0.86	0.01	0.85	0.87
	3	2477	194	0.81	0.01	0.80	0.83	750	54	0.85	0.01	0.83	0.87	1727	140	0.80	0.01	0.78	0.81
	4	2139	170	0.76	0.01	0.74	0.77	646	43	0.80	0.01	0.78	0.83	1493	127	0.74	0.01	0.72	0.76
	5	1842	161	0.70	0.01	0.68	0.71	553	46	0.74	0.01	0.71	0.77	1289	115	0.68	0.01	0.66	0.70
	10	759	374	0.52	0.01	0.50	0.54	212	108	0.55	0.02	0.51	0.59	547	266	0.50	0.01	0.48	0.53

Figure 9: IDFS by number of positive nodes

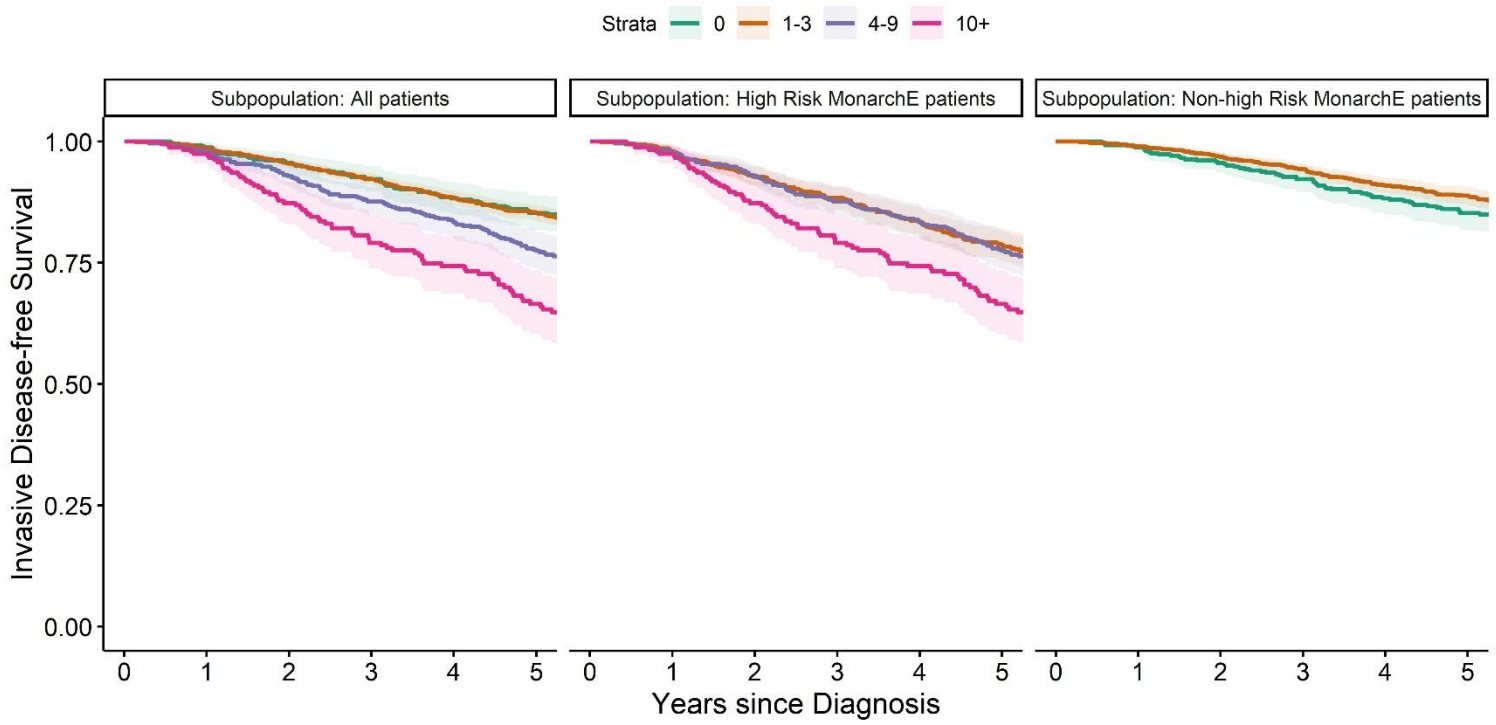


Table 11: IDFS by number of positive nodes

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
pnodes	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
0 n = 412|0|412	1	405	5	0.99	0.01	0.98	1.00							405	5	0.99	0.01	0.98	1.00
	2	379	13	0.96	0.01	0.94	0.98							379	13	0.96	0.01	0.94	0.98
	3	354	13	0.92	0.01	0.90	0.95							354	13	0.92	0.01	0.90	0.95
	4	331	15	0.88	0.02	0.85	0.92							331	15	0.88	0.02	0.85	0.92
	5	301	11	0.85	0.02	0.82	0.89							301	11	0.85	0.02	0.82	0.89
	10	149	39	0.71	0.03	0.66	0.77							149	39	0.71	0.03	0.66	0.77
1-3 n = 2146|721|1425	1	2062	28	0.99	0.00	0.98	0.99	691	14	0.98	0.01	0.97	0.99	1371	14	0.99	0.00	0.98	1.00
	2	1838	65	0.95	0.00	0.95	0.96	608	36	0.93	0.01	0.91	0.95	1230	29	0.97	0.00	0.96	0.98
	3	1635	58	0.92	0.01	0.91	0.94	530	28	0.88	0.01	0.86	0.91	1105	30	0.94	0.01	0.93	0.96
	4	1429	66	0.88	0.01	0.87	0.90	462	28	0.83	0.01	0.81	0.86	967	38	0.91	0.01	0.89	0.93
	5	1268	47	0.85	0.01	0.84	0.87	394	25	0.79	0.02	0.76	0.82	874	22	0.89	0.01	0.87	0.91
	10	554	171	0.70	0.01	0.68	0.73	169	58	0.64	0.02	0.60	0.69	385	113	0.73	0.02	0.70	0.76
4-9 n = 535|535|0	1	507	11	0.98	0.01	0.97	0.99	507	11	0.98	0.01	0.97	0.99						
	2	449	25	0.93	0.01	0.91	0.95	449	25	0.93	0.01	0.91	0.95						
	3	391	25	0.88	0.01	0.85	0.91	391	25	0.88	0.01	0.85	0.91						
	4	339	18	0.83	0.02	0.80	0.87	339	18	0.83	0.02	0.80	0.87						
	5	293	23	0.77	0.02	0.74	0.81	293	23	0.77	0.02	0.74	0.81						
	10	123	59	0.58	0.03	0.53	0.63	123	59	0.58	0.03	0.53	0.63						
10+ n = 242|242|0	1	228	6	0.97	0.01	0.96	0.99	228	6	0.97	0.01	0.96	0.99						
	2	191	23	0.87	0.02	0.83	0.92	191	23	0.87	0.02	0.83	0.92						
	3	154	17	0.79	0.03	0.74	0.85	154	17	0.79	0.03	0.74	0.85						
	4	139	9	0.74	0.03	0.69	0.80	139	9	0.74	0.03	0.69	0.80						
	5	117	14	0.67	0.03	0.60	0.73	117	14	0.67	0.03	0.60	0.73						
	10	41	26	0.48	0.04	0.40	0.56	41	26	0.48	0.04	0.40	0.56						

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
pnodes	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Missing n = 1265|0|1265	1	1076	159	0.87	0.01	0.85	0.89							1076	159	0.87	0.01	0.85	0.89
	2	878	148	0.75	0.01	0.73	0.77							878	148	0.75	0.01	0.73	0.77
	3	724	108	0.65	0.01	0.63	0.68							724	108	0.65	0.01	0.63	0.68
	4	610	90	0.57	0.01	0.54	0.60							610	90	0.57	0.01	0.54	0.60
	5	499	89	0.49	0.01	0.46	0.52							499	89	0.49	0.01	0.46	0.52
	10	242	157	0.31	0.01	0.29	0.34							242	157	0.31	0.01	0.29	0.34

Figure 10: IDFS by tumour size

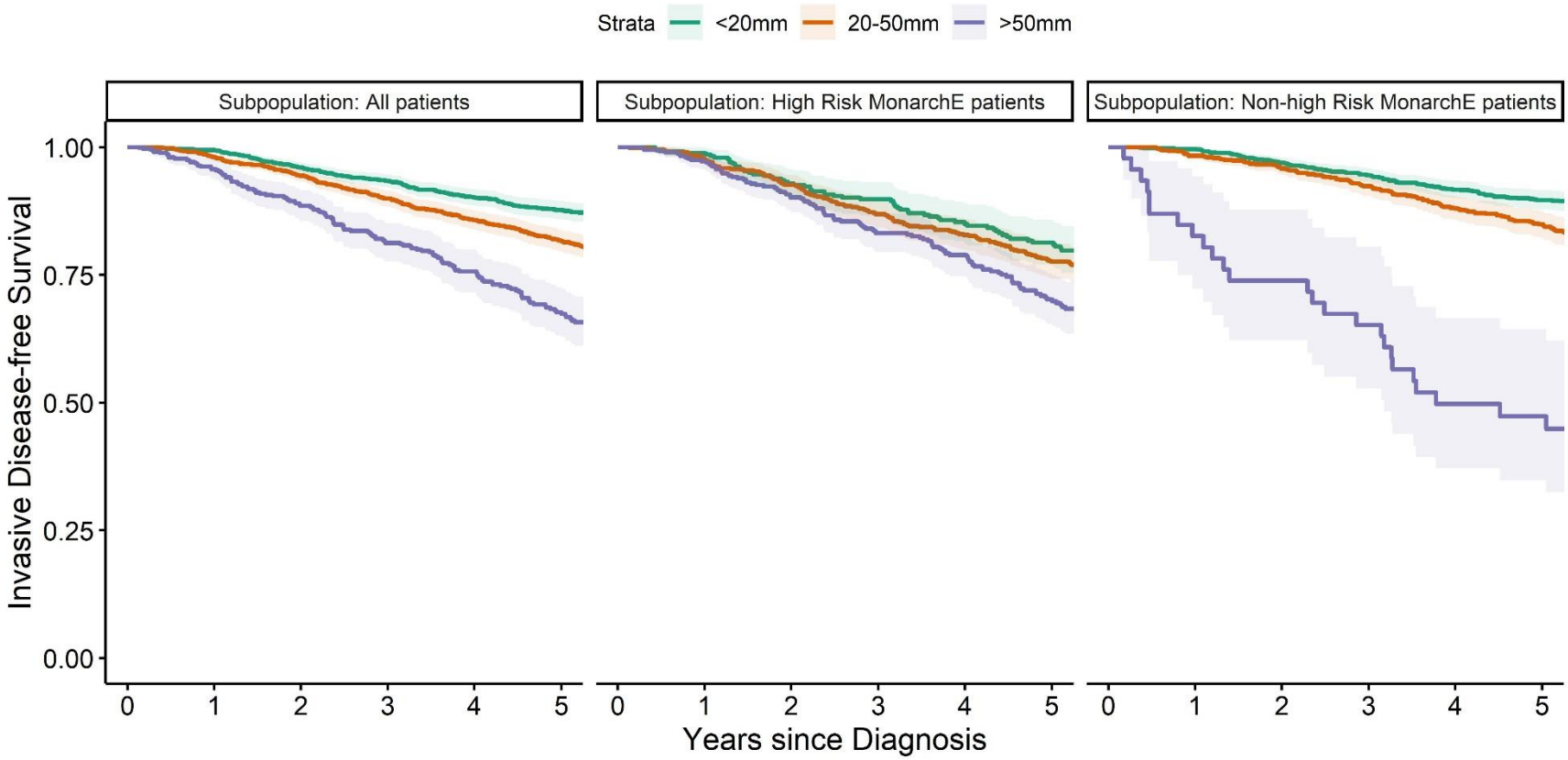


Table 12: IDFS by tumour size

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
size	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
<20mm n = 1517|351|1166	1	1475	8	0.99	0.00	0.99	1.00	340	4	0.99	0.01	0.98	1.00	1135	4	1.00	0.00	0.99	1.00
	2	1351	50	0.96	0.01	0.95	0.97	306	20	0.93	0.01	0.90	0.96	1045	30	0.97	0.01	0.96	0.98
	3	1230	35	0.93	0.01	0.92	0.95	270	10	0.90	0.02	0.87	0.93	960	25	0.95	0.01	0.93	0.96
	4	1104	42	0.90	0.01	0.89	0.92	240	14	0.85	0.02	0.81	0.89	864	28	0.92	0.01	0.90	0.93
	5	1016	29	0.88	0.01	0.86	0.90	216	10	0.81	0.02	0.77	0.86	800	19	0.90	0.01	0.88	0.92
	10	486	128	0.73	0.01	0.71	0.76	103	37	0.65	0.03	0.59	0.71	383	91	0.76	0.02	0.73	0.79
20-50mm n = 1563|702|861	1	1495	30	0.98	0.00	0.97	0.99	666	16	0.98	0.01	0.97	0.99	829	14	0.98	0.00	0.98	0.99
	2	1316	53	0.94	0.01	0.93	0.96	573	33	0.93	0.01	0.91	0.95	743	20	0.96	0.01	0.95	0.97
	3	1152	60	0.90	0.01	0.88	0.92	491	34	0.87	0.01	0.84	0.90	661	26	0.92	0.01	0.91	0.94
	4	1012	52	0.86	0.01	0.84	0.88	426	22	0.83	0.02	0.80	0.86	586	30	0.88	0.01	0.86	0.90
	5	897	46	0.82	0.01	0.80	0.84	374	26	0.78	0.02	0.74	0.81	523	20	0.85	0.01	0.82	0.88
	10	391	150	0.64	0.02	0.61	0.67	142	63	0.60	0.02	0.56	0.65	249	87	0.67	0.02	0.63	0.71
>50mm n = 452|405|47	1	420	19	0.96	0.01	0.94	0.98	382	11	0.97	0.01	0.96	0.99	38	8	0.83	0.06	0.72	0.94
	2	369	31	0.89	0.02	0.86	0.92	335	27	0.90	0.02	0.87	0.93	34	4	0.74	0.06	0.62	0.88
	3	312	29	0.81	0.02	0.78	0.85	282	25	0.83	0.02	0.79	0.87	30	4	0.65	0.07	0.53	0.81
	4	271	21	0.76	0.02	0.72	0.80	249	14	0.79	0.02	0.75	0.83	22	7	0.50	0.07	0.37	0.67
	5	213	27	0.68	0.02	0.63	0.73	194	26	0.70	0.03	0.65	0.75	19	1	0.47	0.07	0.35	0.64
	10	87	43	0.50	0.03	0.44	0.56	76	37	0.52	0.03	0.46	0.59	11	6	0.32	0.07	0.21	0.50
Missing n = 1068|40|1028	1	888	152	0.86	0.01	0.83	0.88	38	0	1.00	0.00	1.00	1.00	850	152	0.85	0.01	0.83	0.87
	2	699	140	0.72	0.01	0.69	0.74	34	4	0.89	0.05	0.80	1.00	665	136	0.71	0.01	0.68	0.74
	3	564	97	0.61	0.02	0.58	0.65	32	1	0.87	0.05	0.77	0.98	532	96	0.60	0.02	0.57	0.64
	4	461	83	0.52	0.02	0.49	0.55	25	5	0.72	0.07	0.59	0.89	436	78	0.51	0.02	0.48	0.55
	5	352	82	0.43	0.02	0.39	0.46	20	0	0.72	0.07	0.59	0.89	332	82	0.41	0.02	0.38	0.45
	10	145	131	0.25	0.02	0.22	0.28	12	6	0.50	0.09	0.34	0.72	133	125	0.24	0.02	0.21	0.27

Figure 11: IDFS by PR status

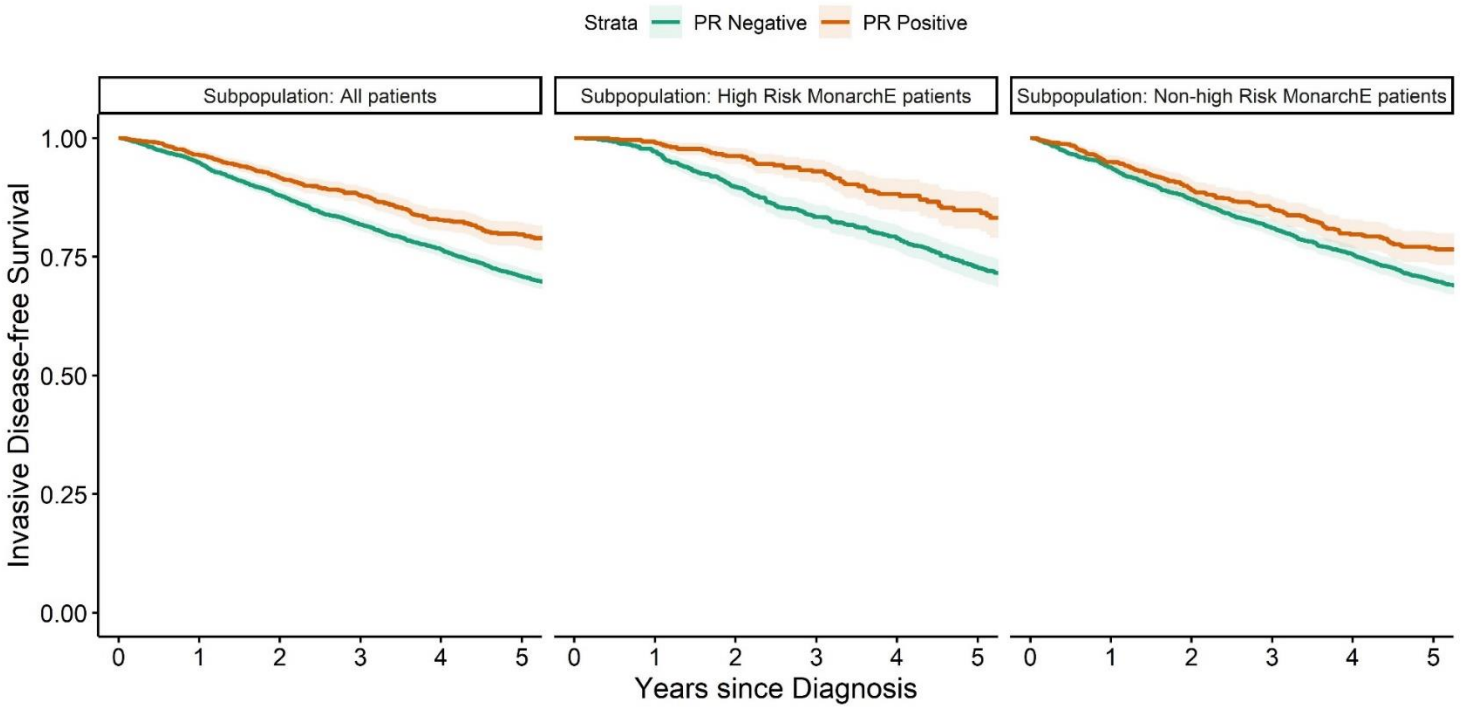


Table 13: IDFS by PR status

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Prstatus	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Negative	1	2864	155	0.95	0.00	0.94	0.96	910	26	0.97	0.01	0.96	0.98	1954	129	0.94	0.01	0.93	0.95
	2	2623	210	0.88	0.01	0.87	0.89	823	70	0.90	0.01	0.88	0.92	1800	140	0.87	0.01	0.86	0.89
	3	2410	180	0.82	0.01	0.80	0.83	748	57	0.83	0.01	0.81	0.86	1662	123	0.81	0.01	0.79	0.83
	4	2236	154	0.77	0.01	0.75	0.78	702	40	0.79	0.01	0.76	0.82	1534	114	0.76	0.01	0.74	0.77
	5	2044	164	0.71	0.01	0.69	0.73	641	54	0.73	0.01	0.70	0.76	1403	110	0.70	0.01	0.68	0.72
	10	1026	400	0.55	0.01	0.53	0.57	303	117	0.57	0.02	0.54	0.61	723	283	0.54	0.01	0.52	0.56
Positive	1	1414	54	0.96	0.00	0.96	0.97	516	5	0.99	0.00	0.98	1.00	898	49	0.95	0.01	0.94	0.96
	2	1112	64	0.92	0.01	0.90	0.93	425	14	0.96	0.01	0.95	0.98	687	50	0.89	0.01	0.87	0.91
	3	848	41	0.88	0.01	0.86	0.90	327	13	0.93	0.01	0.91	0.95	521	28	0.85	0.01	0.83	0.88
	4	612	44	0.83	0.01	0.81	0.85	238	15	0.88	0.02	0.85	0.92	374	29	0.80	0.02	0.77	0.83
	5	434	20	0.80	0.01	0.77	0.82	163	8	0.85	0.02	0.81	0.89	271	12	0.77	0.02	0.74	0.80
	10	83	52	0.60	0.03	0.55	0.66	30	26	0.60	0.05	0.52	0.70	53	26	0.60	0.03	0.53	0.67

Figure 12: IDFS by tumour grade

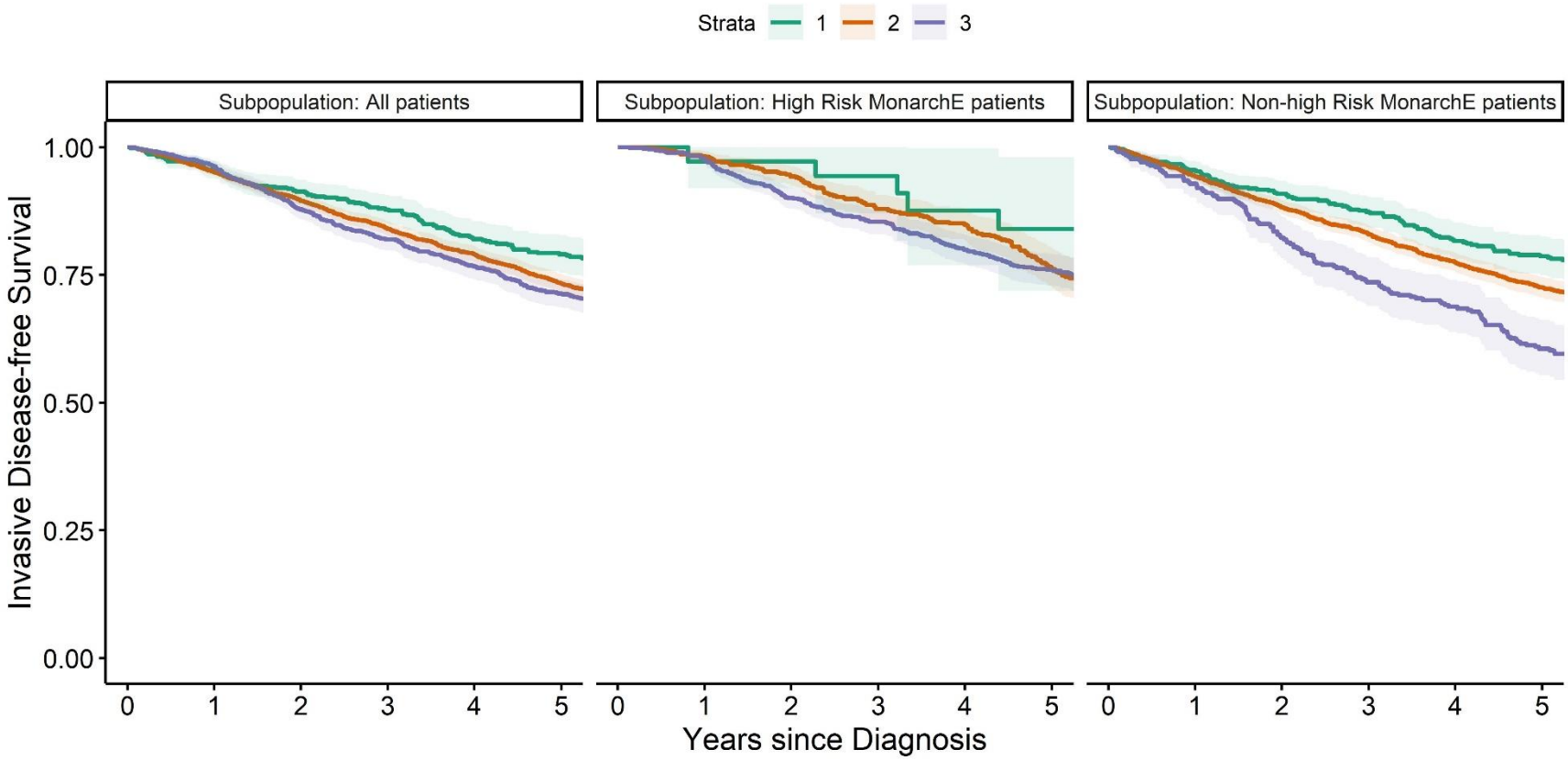


Table 14: IDFS by grade

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Grade	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
1	1	516	24	0.96	0.01	0.94	0.97	35	1	0.97	0.03	0.92	1.00	481	23	0.96	0.01	0.94	0.97
	2	466	23	0.91	0.01	0.89	0.94	34	0	0.97	0.03	0.92	1.00	432	23	0.91	0.01	0.88	0.93
	3	407	17	0.88	0.01	0.85	0.91	30	1	0.94	0.04	0.87	1.00	377	16	0.87	0.02	0.84	0.90
	4	361	26	0.82	0.02	0.79	0.85	26	2	0.88	0.06	0.77	1.00	335	24	0.82	0.02	0.78	0.85
	5	331	13	0.79	0.02	0.75	0.83	23	1	0.84	0.07	0.72	0.98	308	12	0.79	0.02	0.75	0.83
	10	154	58	0.62	0.03	0.57	0.67	<10	5	0.58	0.11	0.40	0.84	146	53	0.62	0.03	0.57	0.67
2	1	2575	132	0.95	0.00	0.94	0.96	562	10	0.98	0.01	0.97	0.99	2013	122	0.94	0.00	0.93	0.95
	2	2249	148	0.90	0.01	0.88	0.91	502	22	0.94	0.01	0.92	0.96	1747	126	0.88	0.01	0.87	0.90
	3	1970	133	0.84	0.01	0.83	0.85	428	33	0.88	0.01	0.85	0.91	1542	100	0.83	0.01	0.81	0.85
	4	1712	113	0.79	0.01	0.77	0.81	378	14	0.85	0.02	0.82	0.88	1334	99	0.78	0.01	0.76	0.79
	5	1471	118	0.73	0.01	0.72	0.75	309	36	0.76	0.02	0.73	0.80	1162	82	0.73	0.01	0.71	0.75
	10	636	273	0.56	0.01	0.54	0.58	116	60	0.56	0.03	0.51	0.62	520	213	0.56	0.01	0.53	0.58
3	1	1135	44	0.96	0.01	0.95	0.97	823	20	0.98	0.01	0.97	0.99	312	24	0.93	0.01	0.90	0.96
	2	975	97	0.88	0.01	0.86	0.90	706	62	0.90	0.01	0.88	0.92	269	35	0.82	0.02	0.78	0.86
	3	845	63	0.82	0.01	0.80	0.84	612	35	0.85	0.01	0.83	0.88	233	28	0.74	0.02	0.69	0.78
	4	745	53	0.77	0.01	0.74	0.79	532	38	0.80	0.01	0.77	0.83	213	15	0.69	0.03	0.64	0.74
	5	649	50	0.71	0.01	0.69	0.74	468	25	0.76	0.02	0.73	0.79	181	25	0.61	0.03	0.55	0.66
	10	304	115	0.56	0.02	0.53	0.60	206	77	0.61	0.02	0.57	0.65	98	38	0.46	0.03	0.41	0.52
Unknown	1	52	9	0.85	0.04	0.77	0.95	<10	0	1.00	0.00	1.00	1.00	46	9	0.84	0.05	0.75	0.94
	2	45	6	0.76	0.05	0.66	0.87	<10	0	1.00	0.00	1.00	1.00	39	6	0.73	0.06	0.62	0.86
	3	36	8	0.62	0.06	0.51	0.76	<10	1	0.83	0.15	0.58	1.00	31	7	0.60	0.07	0.48	0.74
	4	30	6	0.52	0.06	0.40	0.66	<10	1	0.67	0.19	0.38	1.00	26	5	0.50	0.07	0.38	0.65
	5	27	3	0.46	0.06	0.35	0.61	<10	0	0.67	0.19	0.38	1.00	23	3	0.44	0.07	0.33	0.60
	10	15	6	0.35	0.06	0.25	0.50	<10	1	0.50	0.20	0.22	1.00	12	5	0.34	0.07	0.23	0.50

Figure 13: IDFS by age group

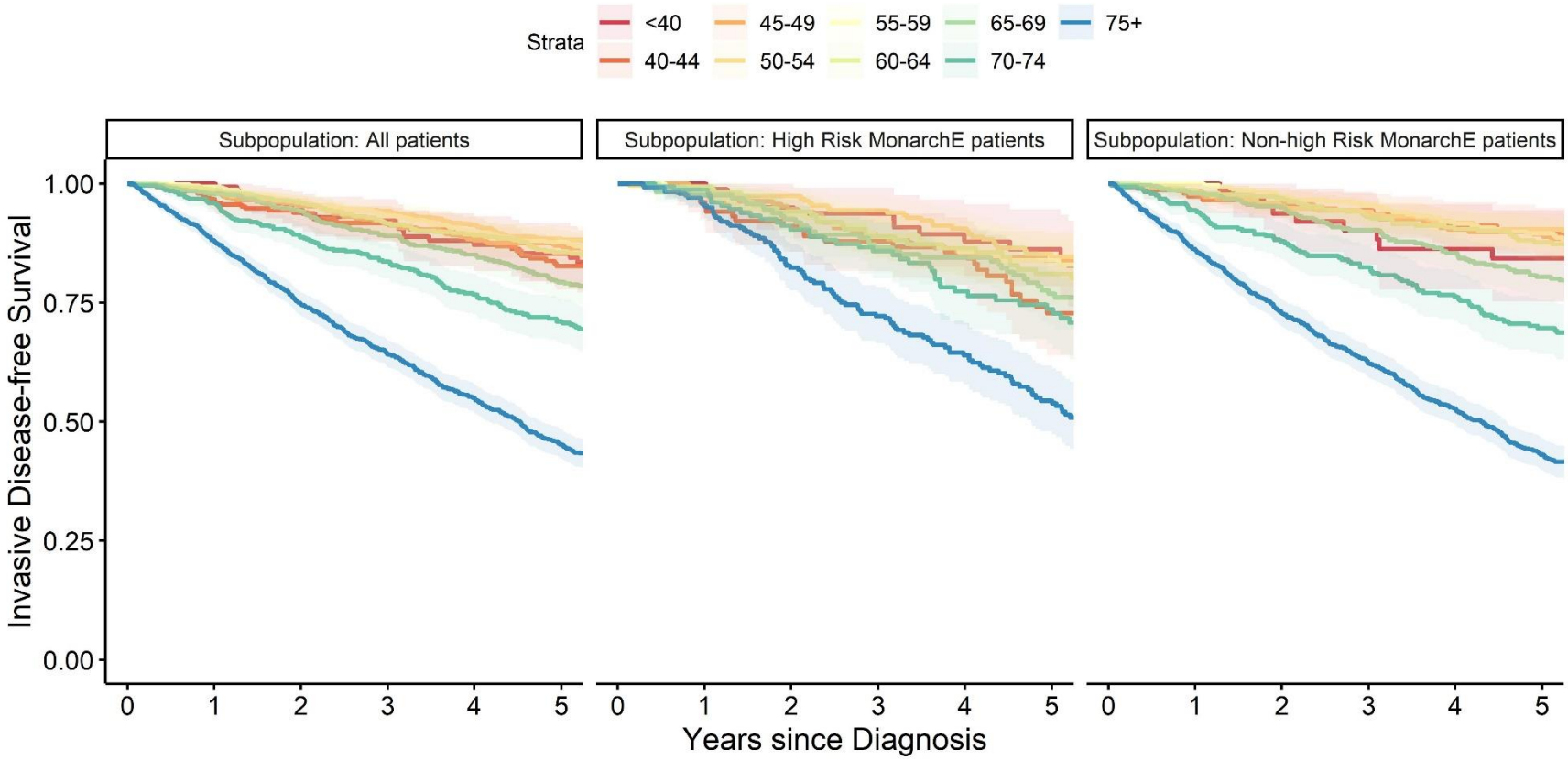


Table 15: IDFS by age group

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Age	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
<40	1	149	0	1.00	0.00	1.00	1.00	81	0	1.00	0.00	1.00	1.00	68	0	1.00	0.00	1.00	1.00
	2	130	8	0.94	0.02	0.91	0.98	74	4	0.95	0.02	0.90	1.00	56	4	0.94	0.03	0.88	1.00
	3	112	3	0.92	0.02	0.88	0.97	65	1	0.94	0.03	0.88	0.99	47	2	0.90	0.04	0.83	0.98
	4	101	6	0.87	0.03	0.82	0.93	58	4	0.88	0.04	0.81	0.96	43	2	0.86	0.05	0.78	0.96
	5	91	2	0.85	0.03	0.79	0.92	51	1	0.86	0.04	0.79	0.95	40	1	0.84	0.05	0.75	0.94
	10	39	15	0.68	0.05	0.60	0.78	17	10	0.66	0.07	0.54	0.80	22	5	0.72	0.07	0.60	0.86
40-44	1	241	8	0.97	0.01	0.95	0.99	98	4	0.96	0.02	0.92	1.00	143	4	0.97	0.01	0.95	1.00
	2	219	7	0.94	0.02	0.91	0.97	86	5	0.91	0.03	0.86	0.97	133	2	0.96	0.02	0.93	0.99
	3	195	5	0.92	0.02	0.88	0.95	75	3	0.88	0.03	0.82	0.95	120	2	0.94	0.02	0.91	0.98
	4	182	6	0.89	0.02	0.85	0.93	72	2	0.86	0.04	0.79	0.93	110	4	0.91	0.02	0.86	0.96
	5	152	12	0.83	0.03	0.78	0.88	55	10	0.73	0.05	0.64	0.83	97	2	0.89	0.03	0.84	0.95
	10	80	22	0.68	0.04	0.62	0.76	24	12	0.54	0.06	0.44	0.67	56	10	0.78	0.04	0.70	0.87
45-49	1	434	7	0.98	0.01	0.97	1.00	185	3	0.98	0.01	0.97	1.00	249	4	0.98	0.01	0.97	1.00
	2	399	13	0.95	0.01	0.93	0.97	169	7	0.95	0.02	0.91	0.98	230	6	0.96	0.01	0.94	0.98
	3	361	16	0.91	0.01	0.89	0.94	146	10	0.89	0.02	0.84	0.94	215	6	0.93	0.02	0.90	0.97
	4	325	13	0.88	0.02	0.85	0.91	130	6	0.85	0.03	0.80	0.91	195	7	0.90	0.02	0.87	0.94
	5	299	4	0.87	0.02	0.84	0.90	115	2	0.84	0.03	0.78	0.89	184	2	0.89	0.02	0.85	0.93
	10	154	31	0.76	0.02	0.71	0.81	56	11	0.74	0.04	0.67	0.82	98	20	0.77	0.03	0.72	0.84
50-54	1	571	8	0.99	0.00	0.98	1.00	222	3	0.99	0.01	0.97	1.00	349	5	0.99	0.01	0.97	1.00
	2	513	15	0.96	0.01	0.94	0.98	201	3	0.97	0.01	0.95	0.99	312	12	0.95	0.01	0.93	0.97
	3	469	9	0.94	0.01	0.92	0.96	179	6	0.94	0.02	0.91	0.98	290	3	0.94	0.01	0.92	0.97
	4	420	14	0.91	0.01	0.89	0.94	157	7	0.91	0.02	0.87	0.95	263	7	0.92	0.02	0.89	0.95
	5	381	14	0.88	0.01	0.85	0.91	137	10	0.85	0.03	0.80	0.90	244	4	0.90	0.02	0.87	0.94
	10	184	32	0.78	0.02	0.74	0.82	59	11	0.75	0.04	0.68	0.82	125	21	0.80	0.03	0.75	0.85

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Age	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
55-59	1	465	3	0.99	0.00	0.99	1.00	153	3	0.98	0.01	0.96	1.00	312	0	1.00	0.00	1.00	1.00
	2	409	15	0.96	0.01	0.94	0.98	132	7	0.93	0.02	0.90	0.97	277	8	0.97	0.01	0.96	0.99
	3	369	11	0.93	0.01	0.91	0.96	115	6	0.89	0.03	0.84	0.94	254	5	0.96	0.01	0.93	0.98
	4	327	14	0.90	0.02	0.87	0.93	101	4	0.86	0.03	0.80	0.92	226	10	0.92	0.02	0.88	0.95
	5	298	7	0.88	0.02	0.84	0.91	90	2	0.84	0.03	0.78	0.90	208	5	0.90	0.02	0.86	0.93
	10	157	30	0.77	0.02	0.72	0.81	44	8	0.74	0.04	0.66	0.83	113	22	0.78	0.03	0.72	0.84
60-64	1	447	6	0.99	0.01	0.98	1.00	155	1	0.99	0.01	0.98	1.00	292	5	0.98	0.01	0.97	1.00
	2	410	12	0.96	0.01	0.94	0.98	134	8	0.94	0.02	0.90	0.98	276	4	0.97	0.01	0.95	0.99
	3	368	18	0.92	0.01	0.89	0.94	111	7	0.89	0.03	0.84	0.94	257	11	0.93	0.02	0.90	0.96
	4	336	10	0.89	0.02	0.86	0.92	100	3	0.86	0.03	0.81	0.92	236	7	0.90	0.02	0.87	0.94
	5	307	13	0.86	0.02	0.82	0.89	87	6	0.81	0.03	0.74	0.88	220	7	0.88	0.02	0.84	0.92
	10	160	42	0.71	0.03	0.66	0.76	33	17	0.59	0.05	0.49	0.70	127	25	0.75	0.03	0.70	0.81
65-69	1	493	11	0.98	0.01	0.97	0.99	158	4	0.98	0.01	0.95	1.00	335	7	0.98	0.01	0.97	0.99
	2	450	18	0.94	0.01	0.92	0.96	144	8	0.93	0.02	0.89	0.97	306	10	0.95	0.01	0.93	0.97
	3	397	24	0.89	0.01	0.86	0.92	126	9	0.87	0.03	0.81	0.92	271	15	0.90	0.02	0.87	0.93
	4	360	17	0.85	0.02	0.82	0.88	117	3	0.84	0.03	0.79	0.90	243	14	0.85	0.02	0.82	0.89
	5	317	24	0.79	0.02	0.76	0.83	98	10	0.77	0.04	0.70	0.84	219	14	0.80	0.02	0.76	0.85
	10	151	39	0.66	0.03	0.61	0.71	51	15	0.62	0.04	0.54	0.72	100	24	0.67	0.03	0.62	0.74
70-74	1	414	18	0.96	0.01	0.94	0.98	149	2	0.99	0.01	0.97	1.00	265	16	0.94	0.01	0.92	0.97
	2	356	30	0.89	0.02	0.86	0.92	123	12	0.90	0.02	0.86	0.95	233	18	0.88	0.02	0.84	0.92
	3	311	20	0.84	0.02	0.80	0.87	108	6	0.86	0.03	0.80	0.92	203	14	0.82	0.02	0.78	0.87
	4	267	25	0.77	0.02	0.73	0.81	86	10	0.77	0.04	0.70	0.85	181	15	0.76	0.03	0.71	0.82
	5	229	19	0.71	0.02	0.67	0.76	78	4	0.74	0.04	0.66	0.82	151	15	0.70	0.03	0.64	0.76
	10	93	54	0.50	0.03	0.45	0.56	28	20	0.51	0.05	0.41	0.62	65	34	0.50	0.04	0.44	0.58

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Age	**Years**	**n.risk**	**n.event**	**surv**	**std.err**	**lower**	**upper**	**n.risk**	**n.event**	**surv**	**std.err**	**lower**	**upper**	**n.risk**	**n.event**	**surv**	**std.err**	**lower**	**upper**
75+	1	1064	148	0.88	0.01	0.86	0.90	225	11	0.95	0.01	0.93	0.98	839	137	0.86	0.01	0.84	0.88
	2	849	156	0.75	0.01	0.72	0.77	185	30	0.82	0.03	0.78	0.87	664	126	0.73	0.01	0.70	0.76
	3	676	115	0.64	0.01	0.61	0.67	150	22	0.72	0.03	0.67	0.78	526	93	0.62	0.02	0.59	0.65
	4	530	93	0.55	0.02	0.52	0.58	119	16	0.64	0.03	0.58	0.71	411	77	0.53	0.02	0.49	0.56
	5	404	89	0.45	0.02	0.42	0.48	93	17	0.54	0.04	0.48	0.62	311	72	0.43	0.02	0.40	0.47
	10	91	187	0.19	0.01	0.16	0.22	21	39	0.24	0.04	0.18	0.33	70	148	0.18	0.02	0.15	0.21

Figure 14: IDFS by inflammatory disease

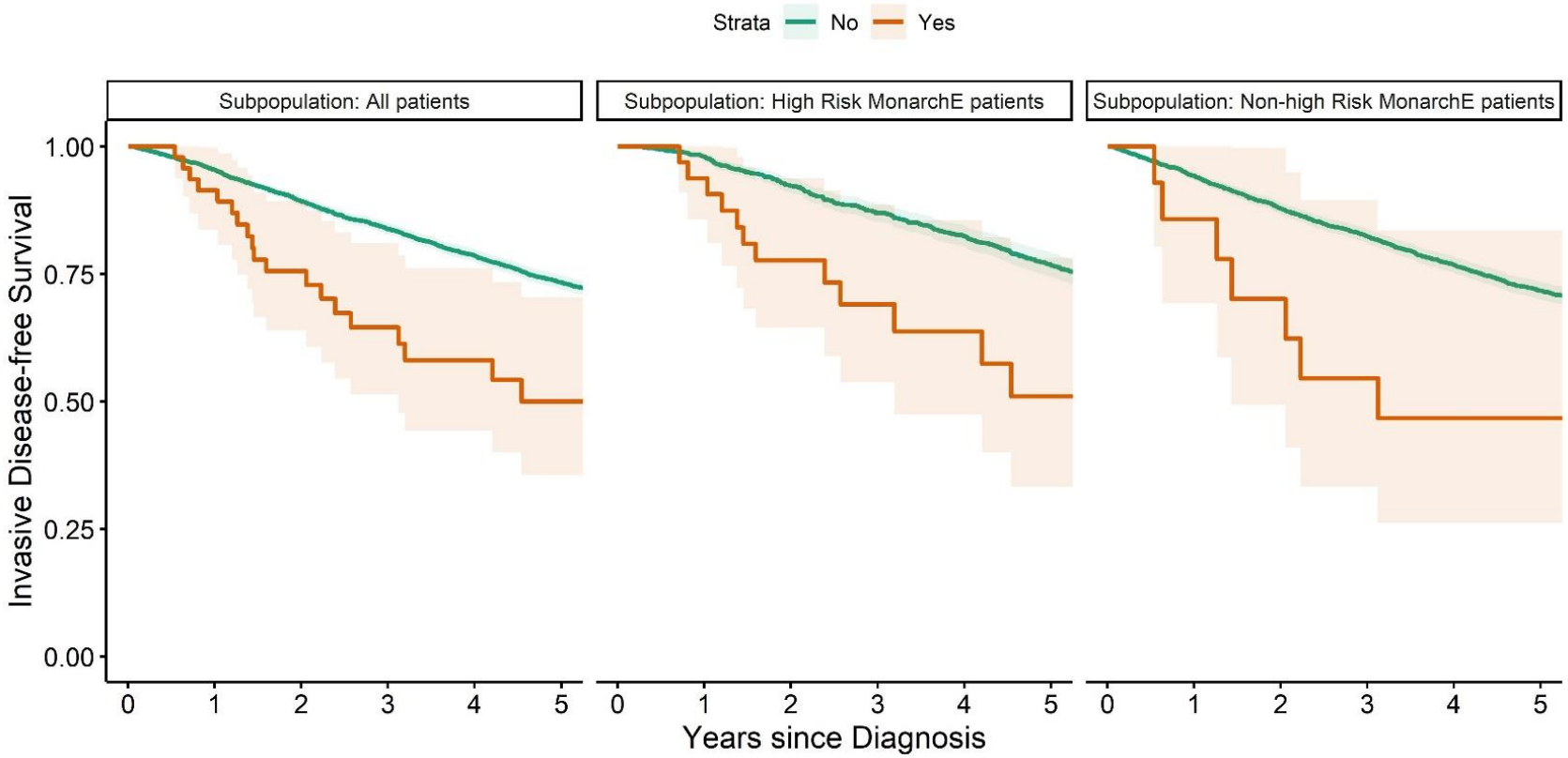


Table 16: IDFS by inflammatory disease status

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Inflam	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
No	1	4236	205	0.95	0.00	0.95	0.96	1396	29	0.98	0.00	0.97	0.99	2840	176	0.94	0.00	0.93	0.95
	2	3706	267	0.89	0.00	0.88	0.90	1228	79	0.92	0.01	0.91	0.94	2478	188	0.88	0.01	0.87	0.89
	3	3238	217	0.84	0.01	0.83	0.85	1062	68	0.87	0.01	0.85	0.89	2176	149	0.82	0.01	0.81	0.84
	4	2831	196	0.79	0.01	0.77	0.80	929	54	0.82	0.01	0.80	0.84	1902	142	0.77	0.01	0.75	0.78
	5	2466	182	0.73	0.01	0.72	0.75	796	60	0.77	0.01	0.74	0.79	1670	122	0.72	0.01	0.70	0.73
	10	1105	450	0.57	0.01	0.55	0.58	331	143	0.59	0.02	0.56	0.62	774	307	0.55	0.01	0.53	0.57
Yes	1	42	4	0.91	0.04	0.84	1.00	30	2	0.94	0.04	0.86	1.00	12	2	0.86	0.09	0.69	1.00
	2	29	7	0.76	0.06	0.64	0.89	20	5	0.78	0.07	0.64	0.94	<10	<10	0.70	0.13	0.49	1.00
	3	20	4	0.65	0.07	0.51	0.81	13	2	0.69	0.09	0.54	0.89	<10	<10	0.55	0.14	0.33	0.90
	4	17	2	0.58	0.08	0.44	0.76	11	1	0.64	0.10	0.47	0.86	<10	<10	0.47	0.14	0.26	0.84
	5	12	2	0.50	0.09	0.36	0.70	<10	2	0.51	0.11	0.33	0.78	<10	<10	0.47	0.14	0.26	0.84
	10	<10	2	0.36	0.10	0.21	0.64	<10	0	0.51	0.11	0.33	0.78	<10	<10	0.23	0.14	0.07	0.73

Figure 15: IDFS pre vs post COVID-19 pandemic

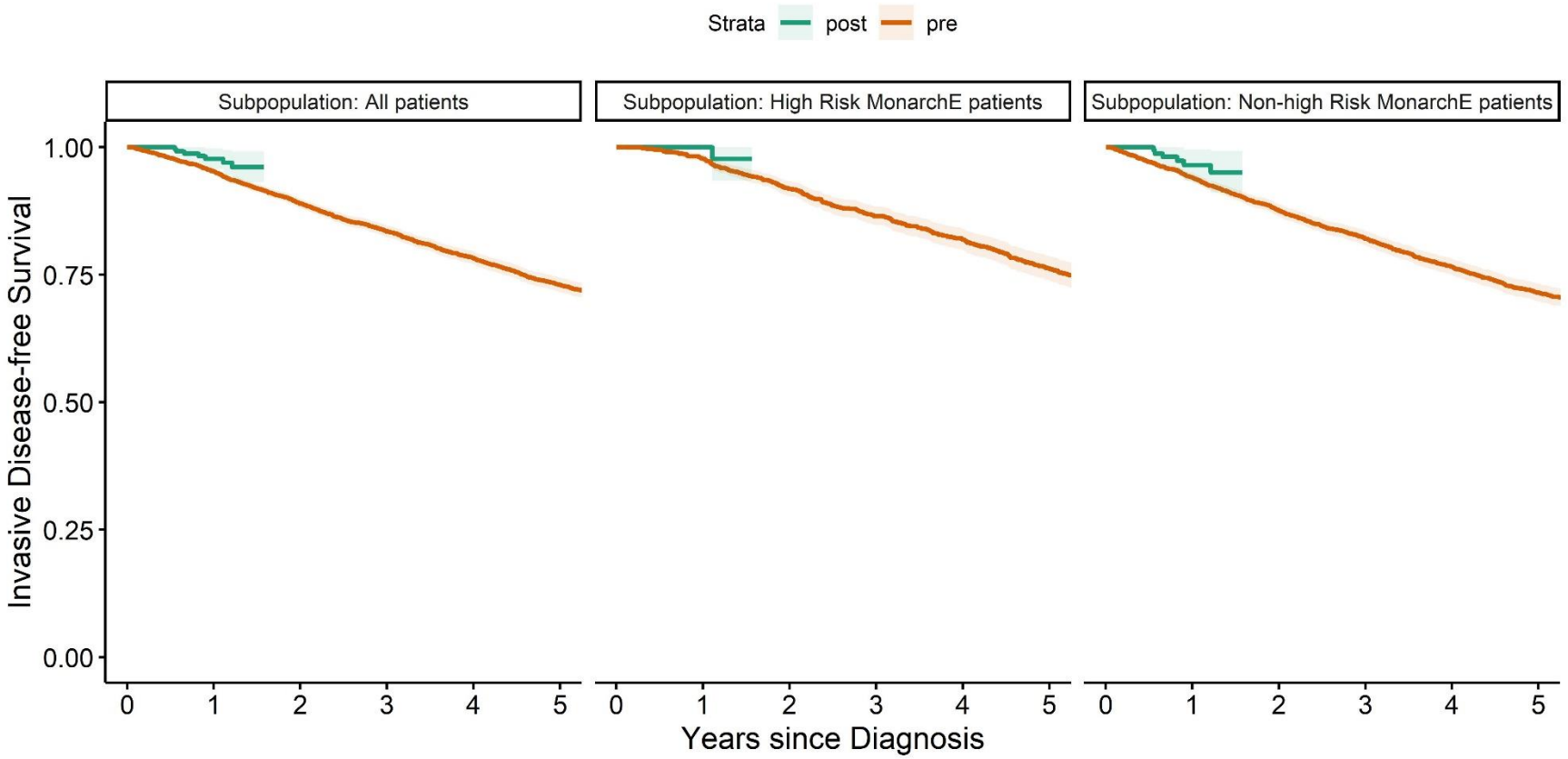


Table 17: IDFS pre vs post COVID pandemic

IDFS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Covid-19 Pandemic	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Post	1	156	5	0.98	0.01	0.96	1.00	55	0	1.00	0.00	1.00	1.00	101	5	0.96	0.02	0.93	1.00
Pre	1	4122	204	0.95	0.00	0.95	0.96	1371	31	0.98	0.00	0.97	0.99	2751	173	0.94	0.00	0.93	0.95
	2	3735	272	0.89	0.00	0.88	0.90	1248	83	0.92	0.01	0.90	0.93	2487	189	0.88	0.01	0.86	0.89
	3	3258	221	0.84	0.01	0.82	0.85	1075	70	0.86	0.01	0.85	0.88	2183	151	0.82	0.01	0.81	0.84
	4	2848	198	0.78	0.01	0.77	0.80	940	55	0.82	0.01	0.80	0.84	1908	143	0.77	0.01	0.75	0.78
	5	2478	184	0.73	0.01	0.72	0.74	804	62	0.76	0.01	0.74	0.79	1674	122	0.72	0.01	0.70	0.73
	10	1109	452	0.56	0.01	0.55	0.58	333	143	0.59	0.02	0.56	0.62	776	309	0.55	0.01	0.53	0.57

6.3.1.1 OS results

Figure 16: OS by Charlson Comorbidity Index

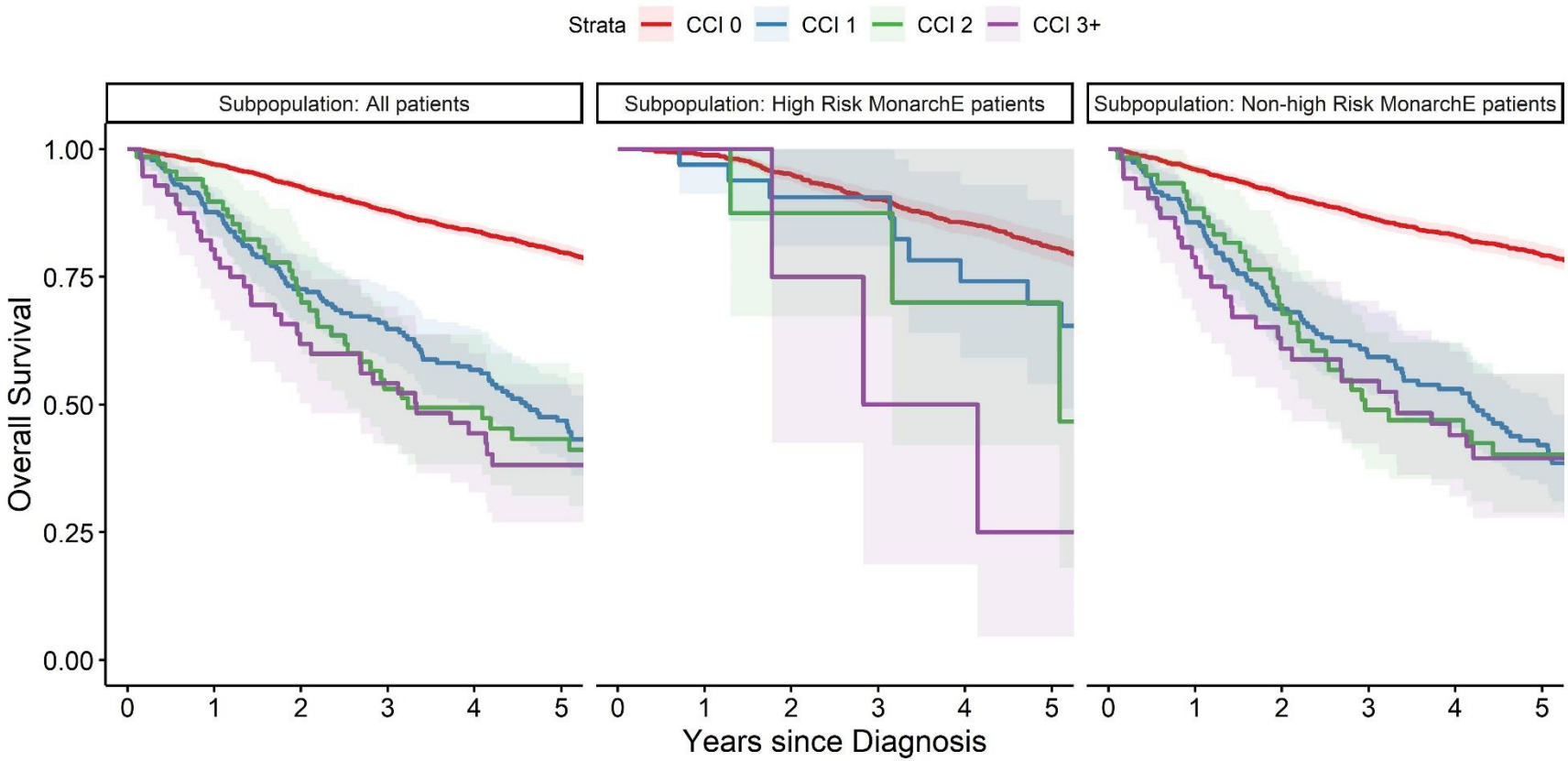


Table 18: OS by comorbidity level

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
CCI	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
0	1	2799	86	0.97	0.00	0.96	0.98	1012	12	0.99	0.00	0.98	0.99	1787	74	0.96	0.00	0.95	0.97
	2	2518	125	0.93	0.00	0.92	0.94	922	38	0.95	0.01	0.94	0.96	1596	87	0.91	0.01	0.90	0.93
	3	2224	123	0.88	0.01	0.87	0.89	805	46	0.90	0.01	0.88	0.92	1419	77	0.87	0.01	0.85	0.88
	4	1977	96	0.84	0.01	0.83	0.85	708	39	0.86	0.01	0.83	0.88	1269	57	0.83	0.01	0.81	0.85
	5	1749	95	0.80	0.01	0.78	0.81	612	38	0.81	0.01	0.78	0.83	1137	57	0.79	0.01	0.77	0.81
	10	835	268	0.65	0.01	0.63	0.67	251	109	0.63	0.02	0.59	0.66	584	159	0.66	0.01	0.63	0.68
1	1	162	23	0.88	0.02	0.83	0.93	32	1	0.97	0.03	0.91	1.00	130	22	0.86	0.03	0.80	0.91
	2	126	27	0.73	0.03	0.66	0.79	27	2	0.91	0.05	0.81	1.00	99	25	0.69	0.04	0.62	0.77
	3	102	13	0.65	0.04	0.58	0.72	24	0	0.91	0.05	0.81	1.00	78	13	0.59	0.04	0.52	0.68
	4	82	12	0.57	0.04	0.50	0.65	18	4	0.74	0.09	0.59	0.93	64	8	0.53	0.04	0.45	0.62
	5	65	14	0.47	0.04	0.40	0.55	16	1	0.70	0.09	0.54	0.90	49	13	0.42	0.04	0.34	0.51
	10	17	28	0.22	0.04	0.16	0.31	<10	3	0.56	0.10	0.40	0.80	10	25	0.15	0.04	0.09	0.24
2	1	61	7	0.90	0.04	0.83	0.97	<10	<10	1.00	0.00	1.00	1.00	53	7	0.88	0.04	0.81	0.97
	2	46	12	0.72	0.06	0.61	0.83	<10	<10	0.88	0.12	0.67	1.00	40	11	0.70	0.06	0.59	0.82
	3	30	11	0.53	0.06	0.42	0.67	<10	<10	0.88	0.12	0.67	1.00	25	11	0.49	0.07	0.37	0.64
	4	25	2	0.49	0.06	0.38	0.64	<10	<10	0.70	0.18	0.42	1.00	22	1	0.47	0.07	0.35	0.62
	5	21	3	0.43	0.07	0.32	0.58	<10	<10	0.70	0.18	0.42	1.00	18	3	0.40	0.07	0.29	0.56
	10	<10	10	0.18	0.06	0.09	0.36							<10	9	0.16	0.06	0.07	0.34
3+	1	45	11	0.80	0.05	0.71	0.91	<10	0	1.00	0.00	1.00	1.00	41	11	0.79	0.06	0.68	0.91
	2	32	10	0.62	0.07	0.50	0.76	<10	<10	0.75	0.22	0.43	1.00	29	9	0.61	0.07	0.49	0.76
	3	28	4	0.54	0.07	0.42	0.69	<10	<10	0.50	0.25	0.19	1.00	26	3	0.55	0.07	0.42	0.70
	4	22	5	0.44	0.07	0.33	0.60	<10	<10	0.50	0.25	0.19	1.00	20	5	0.44	0.07	0.32	0.60
	5	14	3	0.38	0.07	0.27	0.54	<10	<10	0.25	0.22	0.05	1.00	13	2	0.39	0.07	0.28	0.56
	10	<10	9	0.13	0.05	0.05	0.30	<10	<10	0.25	0.22	0.05	1.00	<10	9	0.11	0.06	0.04	0.29

Figure 17: OS by menopausal status

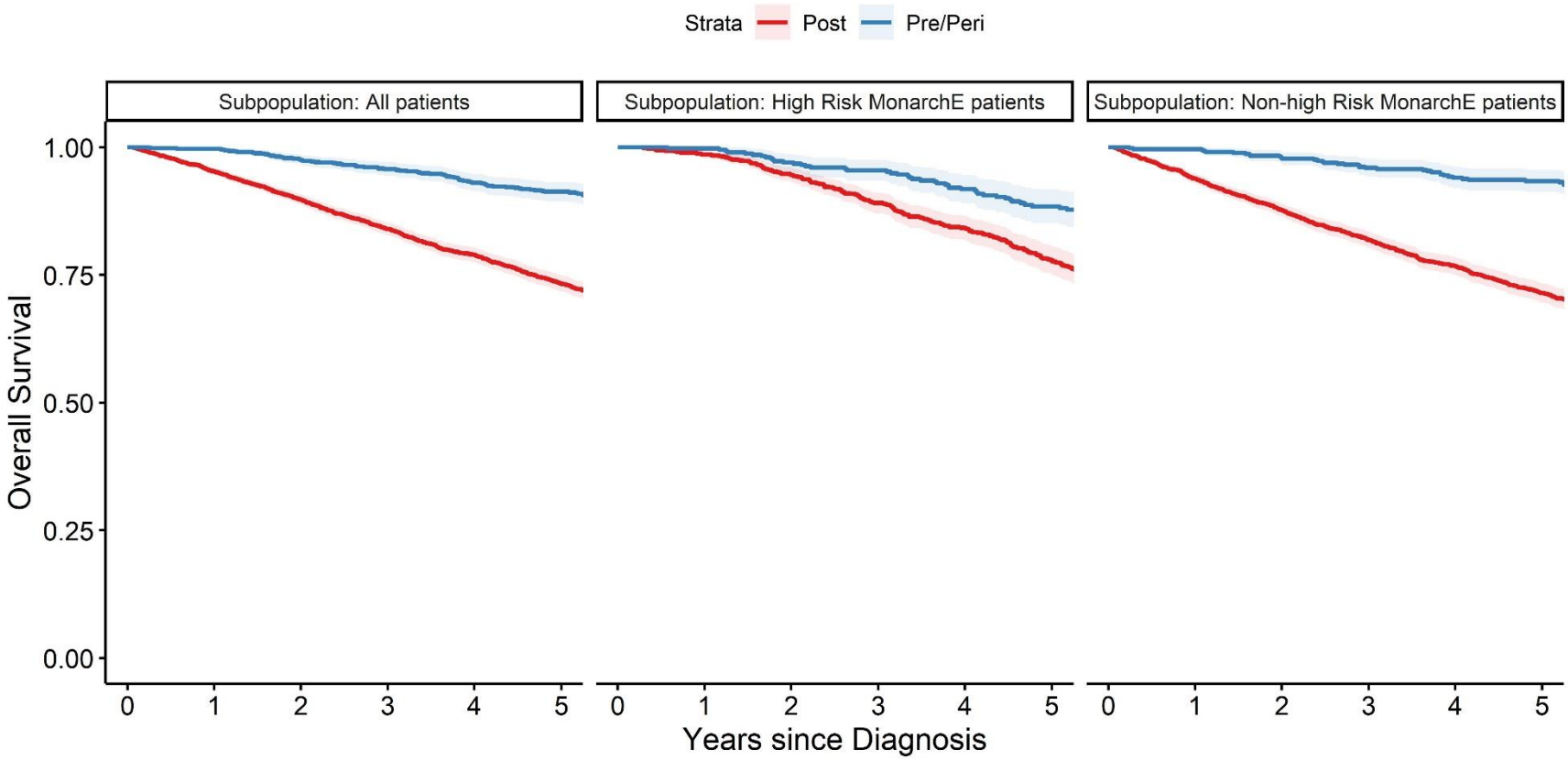


Table 19: OS by menopausal status

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
mstatus	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Pre/Peri	1	965	3	1.00	0.00	0.99	1.00	416	1	1.00	0.00	0.99	1.00	549	2	1.00	0.00	0.99	1.00
	2	890	20	0.98	0.01	0.97	0.99	382	11	0.97	0.01	0.96	0.99	508	9	0.98	0.01	0.97	0.99
	3	816	16	0.96	0.01	0.94	0.97	346	6	0.95	0.01	0.94	0.98	470	10	0.96	0.01	0.94	0.98
	4	749	22	0.93	0.01	0.91	0.95	313	13	0.92	0.01	0.89	0.95	436	9	0.94	0.01	0.92	0.96
	5	683	14	0.91	0.01	0.89	0.93	274	11	0.88	0.02	0.85	0.92	409	3	0.93	0.01	0.91	0.96
	10	395	64	0.81	0.02	0.77	0.83	135	34	0.76	0.03	0.71	0.81	260	30	0.85	0.02	0.80	0.88
Post	1	3351	168	0.95	0.00	0.95	0.96	1025	15	0.99	0.00	0.98	0.99	2326	153	0.94	0.00	0.93	0.95
	2	2947	189	0.90	0.01	0.89	0.91	913	40	0.95	0.01	0.93	0.96	2034	149	0.88	0.01	0.86	0.89
	3	2561	182	0.84	0.01	0.83	0.85	787	51	0.89	0.01	0.87	0.91	1774	131	0.82	0.01	0.80	0.83
	4	2241	149	0.79	0.01	0.78	0.80	684	41	0.84	0.01	0.82	0.87	1557	108	0.77	0.01	0.75	0.78
	5	1946	154	0.73	0.01	0.72	0.75	586	50	0.78	0.01	0.75	0.81	1360	104	0.71	0.01	0.70	0.73
	10	824	382	0.55	0.01	0.53	0.57	230	113	0.58	0.02	0.55	0.62	594	269	0.54	0.01	0.51	0.56

Figure 18: OS by number of positive nodes

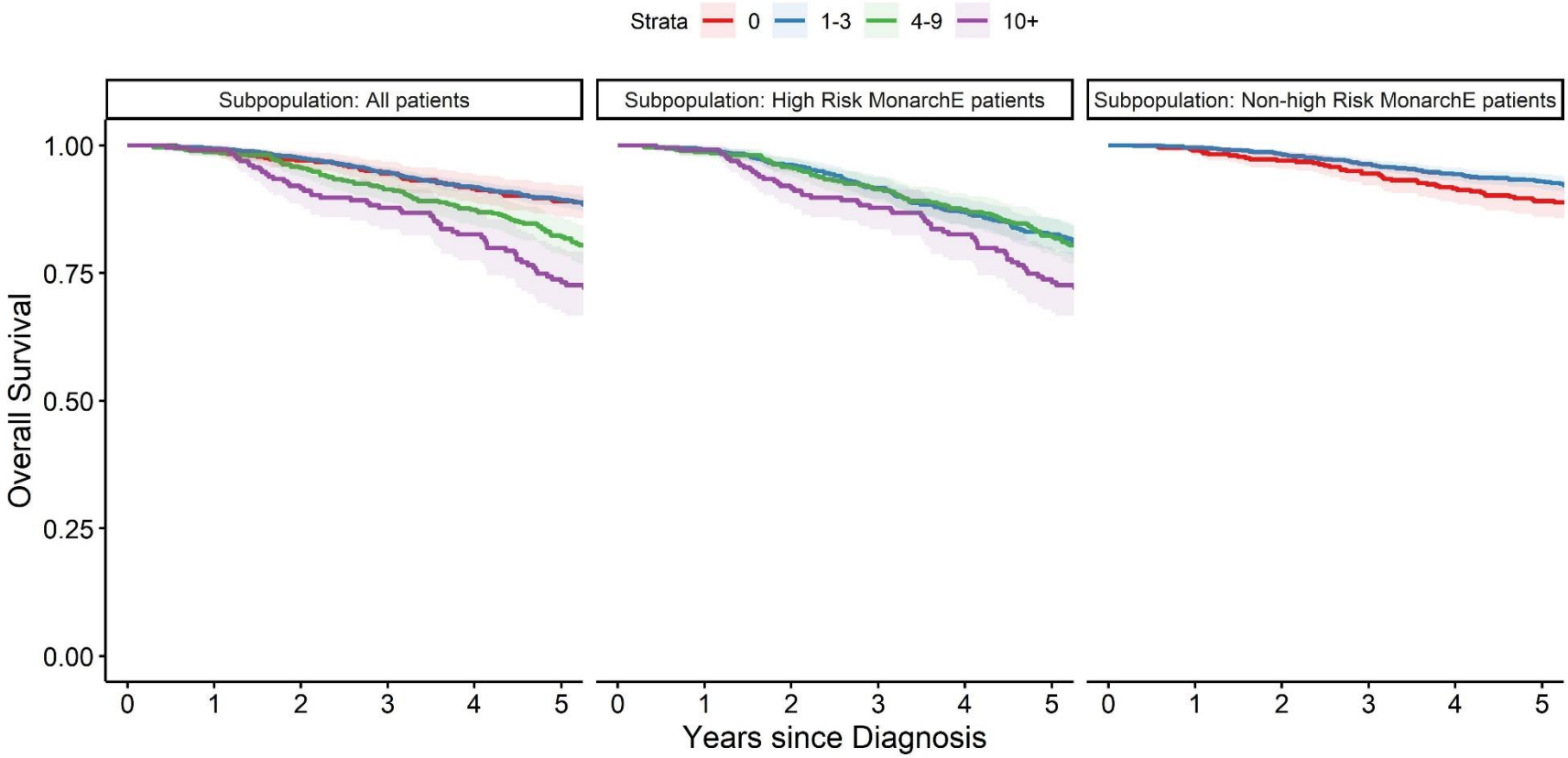


Table 20: OS by number of positive nodes

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
pnodes	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
0 **n = 412|0|412**	1	406	4	0.99	0.00	0.98	1.00							406	4	0.99	0.00	0.98	1.00
	2	385	8	0.97	0.01	0.95	0.99							385	8	0.97	0.01	0.95	0.99
	3	362	10	0.94	0.01	0.92	0.97							362	10	0.94	0.01	0.92	0.97
	4	343	11	0.92	0.01	0.89	0.94							343	11	0.92	0.01	0.89	0.94
	5	315	9	0.89	0.02	0.86	0.92							315	9	0.89	0.02	0.86	0.92
	10	159	39	0.76	0.02	0.71	0.81							159	39	0.76	0.02	0.71	0.81
1-3 **n = 2146|721|1425**	1	2077	13	0.99	0.00	0.99	1.00	698	7	0.99	0.00	0.98	1.00	1379	6	1.00	0.00	0.99	1.00
	2	1882	36	0.98	0.00	0.97	0.98	632	19	0.96	0.01	0.95	0.98	1250	17	0.98	0.00	0.98	0.99
	3	1683	53	0.95	0.01	0.94	0.96	553	29	0.92	0.01	0.90	0.94	1130	24	0.96	0.01	0.95	0.97
	4	1490	49	0.92	0.01	0.91	0.93	484	27	0.87	0.01	0.84	0.90	1006	22	0.94	0.01	0.93	0.96
	5	1334	39	0.89	0.01	0.88	0.91	416	24	0.82	0.02	0.79	0.86	918	15	0.93	0.01	0.91	0.94
	10	612	149	0.76	0.01	0.74	0.78	182	55	0.69	0.02	0.64	0.73	430	94	0.80	0.01	0.77	0.83
4-9 **n = 535|535|0**	1	511	7	0.99	0.00	0.98	1.00	511	7	0.99	0.00	0.98	1.00						
	2	462	15	0.96	0.01	0.94	0.97	462	15	0.96	0.01	0.94	0.97						
	3	408	20	0.91	0.01	0.89	0.94	408	20	0.91	0.01	0.89	0.94						
	4	357	17	0.87	0.02	0.84	0.90	357	17	0.87	0.02	0.84	0.90						
	5	314	20	0.82	0.02	0.79	0.86	314	20	0.82	0.02	0.79	0.86						
	10	137	60	0.63	0.03	0.58	0.68	137	60	0.63	0.03	0.58	0.68						
10+ **n = 242|242|0**	1	232	2	0.99	0.01	0.98	1.00	232	2	0.99	0.01	0.98	1.00						
	2	201	17	0.92	0.02	0.88	0.95	201	17	0.92	0.02	0.88	0.95						
	3	172	8	0.88	0.02	0.84	0.92	172	8	0.88	0.02	0.84	0.92						
	4	156	10	0.83	0.03	0.78	0.88	156	10	0.83	0.03	0.78	0.88						
	5	130	17	0.73	0.03	0.67	0.80	130	17	0.73	0.03	0.67	0.80						
	10	46	32	0.51	0.04	0.43	0.59	46	32	0.51	0.04	0.43	0.59						

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
pnodes	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Missing n = 1265|0|1265	1	1090	145	0.88	0.01	0.87	0.90							1090	145	0.88	0.01	0.87	0.90
	2	907	133	0.77	0.01	0.75	0.80							907	133	0.77	0.01	0.75	0.80
	3	752	107	0.68	0.01	0.65	0.71							752	107	0.68	0.01	0.65	0.71
	4	644	84	0.60	0.01	0.57	0.63							644	84	0.60	0.01	0.57	0.63
	5	536	83	0.52	0.01	0.49	0.55							536	83	0.52	0.01	0.49	0.55
	10	265	166	0.34	0.02	0.31	0.37							265	166	0.34	0.02	0.31	0.37

Figure 19: OS by tumour size

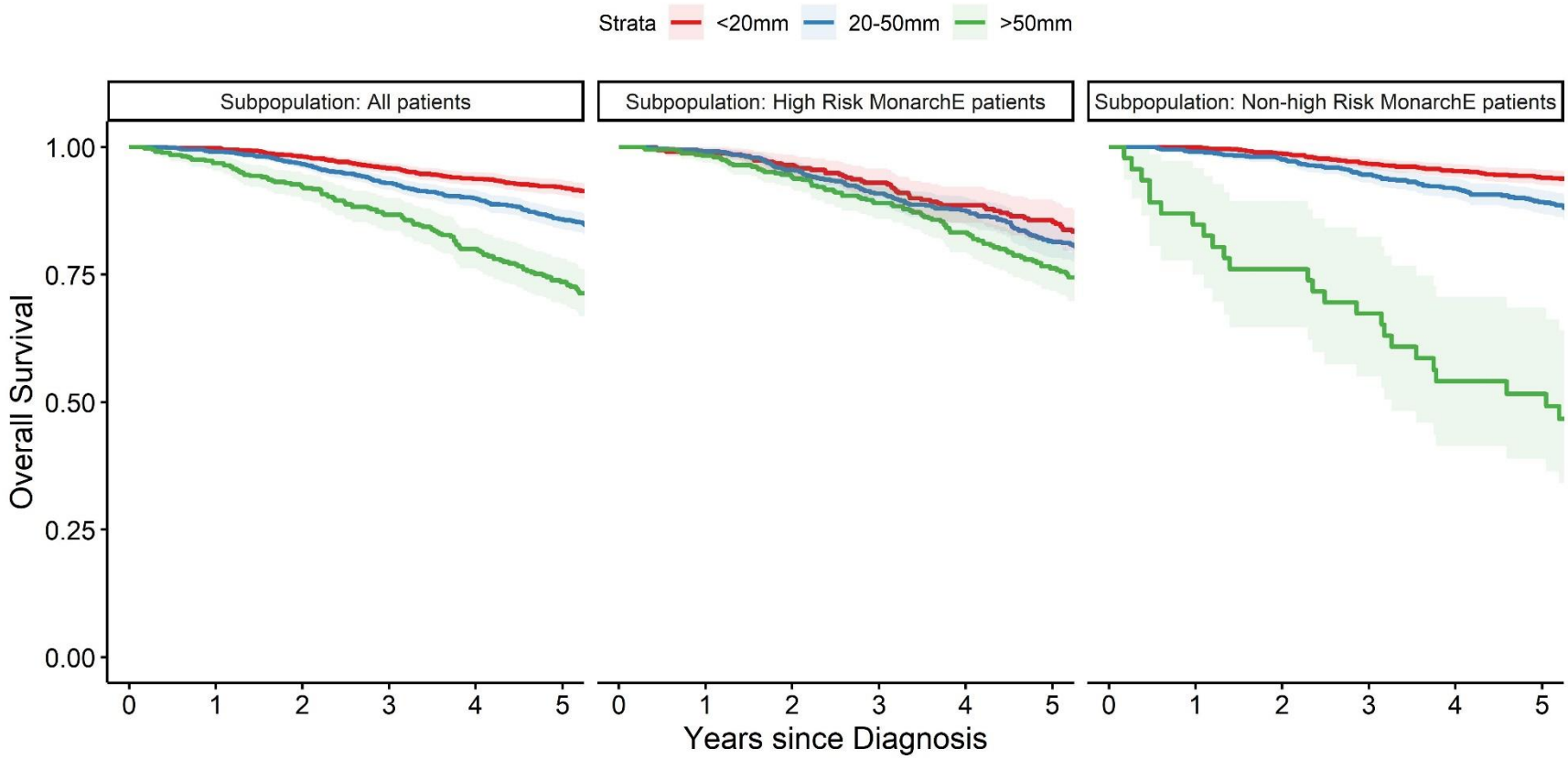


Table 21: OS by tumour size

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
size	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
<20mm n = 1517|351|1166	1	1479	4	1.00	0.00	0.99	1.00	341	3	0.99	0.00	0.98	1.00	1138	1	1.00	0.00	1.00	1.00
	2	1383	22	0.98	0.00	0.98	0.99	318	9	0.96	0.01	0.95	0.98	1065	13	0.99	0.00	0.98	0.99
	3	1264	32	0.96	0.01	0.95	0.97	281	11	0.93	0.01	0.90	0.96	983	21	0.97	0.01	0.96	0.98
	4	1150	27	0.94	0.01	0.92	0.95	251	13	0.89	0.02	0.85	0.92	899	14	0.95	0.01	0.94	0.97
	5	1068	20	0.92	0.01	0.91	0.94	229	8	0.86	0.02	0.82	0.90	839	12	0.94	0.01	0.93	0.95
	10	527	118	0.79	0.01	0.77	0.82	109	40	0.68	0.03	0.62	0.74	418	78	0.82	0.01	0.80	0.85
20-50mm n = 1563|702|861	1	1511	14	0.99	0.00	0.99	1.00	676	6	0.99	0.00	0.98	1.00	835	8	0.99	0.00	0.98	1.00
	2	1349	35	0.97	0.00	0.96	0.98	592	23	0.96	0.01	0.94	0.97	757	12	0.98	0.01	0.97	0.99
	3	1192	50	0.93	0.01	0.92	0.94	516	28	0.91	0.01	0.89	0.93	676	22	0.95	0.01	0.93	0.96
	4	1067	37	0.90	0.01	0.88	0.92	455	18	0.88	0.01	0.85	0.90	612	19	0.92	0.01	0.90	0.94
	5	948	48	0.86	0.01	0.84	0.88	396	31	0.81	0.02	0.78	0.85	552	17	0.89	0.01	0.87	0.92
	10	437	137	0.70	0.01	0.67	0.73	157	59	0.65	0.02	0.61	0.70	280	78	0.73	0.02	0.70	0.77
>50mm n = 452|405|47	1	425	14	0.97	0.01	0.95	0.98	386	7	0.98	0.01	0.97	1.00	39	7	0.85	0.05	0.75	0.96
	2	385	20	0.92	0.01	0.90	0.95	350	16	0.94	0.01	0.92	0.96	35	4	0.76	0.06	0.65	0.89
	3	333	22	0.87	0.02	0.84	0.90	302	18	0.89	0.02	0.86	0.92	31	4	0.67	0.07	0.55	0.82
	4	287	25	0.80	0.02	0.76	0.84	263	19	0.83	0.02	0.79	0.87	24	6	0.54	0.07	0.41	0.71
	5	234	22	0.74	0.02	0.69	0.78	213	21	0.76	0.02	0.72	0.81	21	1	0.52	0.07	0.39	0.69
	10	95	51	0.54	0.03	0.48	0.60	84	43	0.56	0.03	0.50	0.63	11	8	0.32	0.07	0.21	0.50

Figure 20: OS by PR status

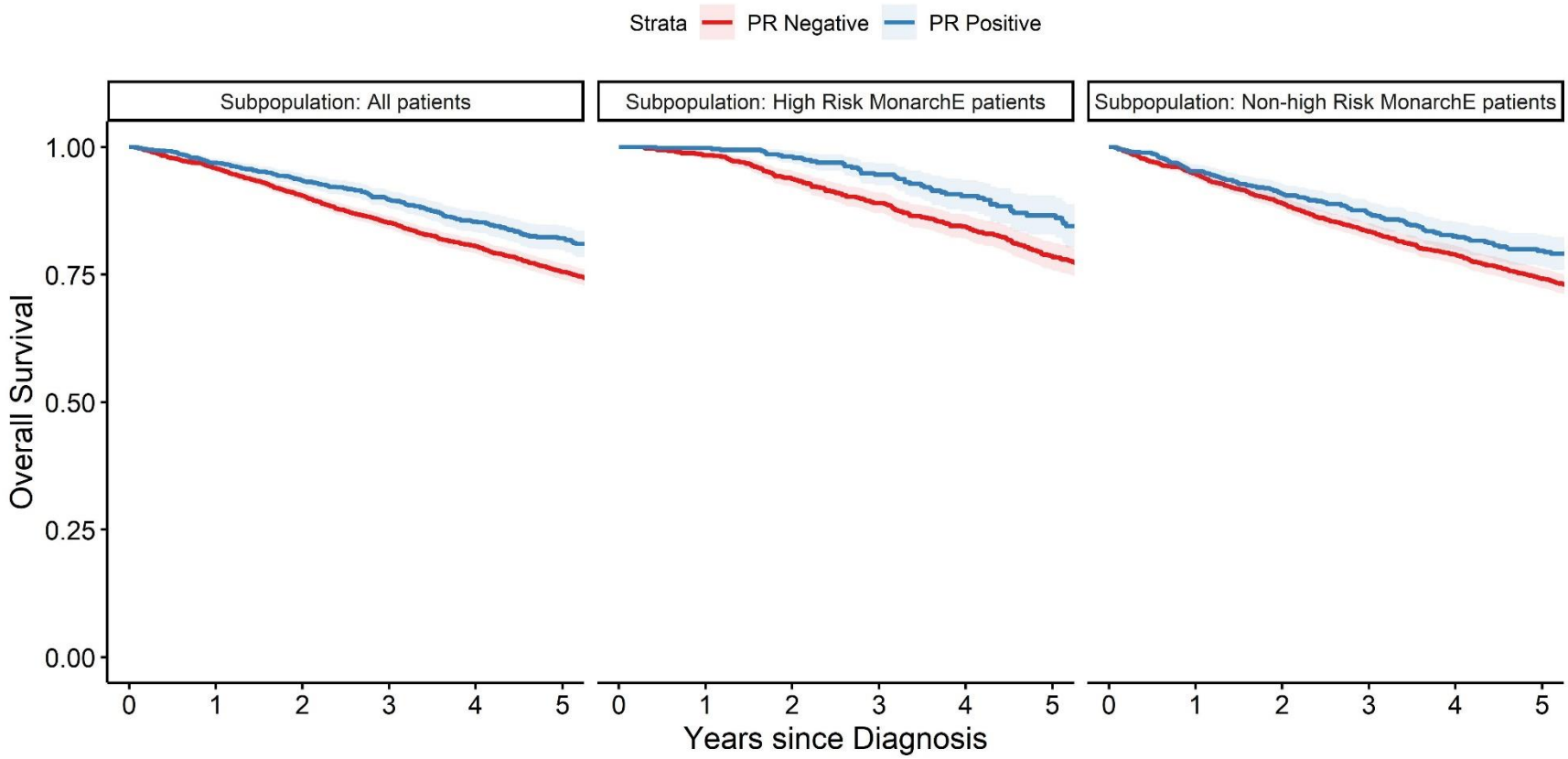


Table 22: OS by PR status

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Prstatus	**Years**	**n.risk**	**n.event**	**surv**	**std.err**	**lower**	**upper**	**n.risk**	**n.event**	**surv**	**std.err**	**lower**	**upper**	**n.risk**	**n.event**	**surv**	**std.err**	**lower**	**upper**
Negative	1	2895	124	0.96	0.00	0.95	0.97	921	15	0.98	0.00	0.98	0.99	1974	109	0.95	0.00	0.94	0.96
	2	2700	163	0.90	0.01	0.89	0.92	860	43	0.94	0.01	0.92	0.95	1840	120	0.89	0.01	0.88	0.90
	3	2510	157	0.85	0.01	0.84	0.86	799	43	0.89	0.01	0.87	0.91	1711	114	0.83	0.01	0.82	0.85
	4	2356	134	0.81	0.01	0.79	0.82	752	41	0.84	0.01	0.82	0.87	1604	93	0.79	0.01	0.77	0.81
	5	2178	147	0.76	0.01	0.74	0.77	691	52	0.79	0.01	0.76	0.81	1487	95	0.74	0.01	0.72	0.76
	10	1133	390	0.60	0.01	0.58	0.62	334	120	0.63	0.02	0.59	0.66	799	270	0.59	0.01	0.57	0.61
Positive	1	1421	47	0.97	0.00	0.96	0.98	520	1	1.00	0.00	0.99	1.00	901	46	0.95	0.01	0.94	0.97
	2	1137	46	0.93	0.01	0.92	0.95	435	8	0.98	0.01	0.97	0.99	702	38	0.91	0.01	0.89	0.93
	3	867	41	0.90	0.01	0.88	0.91	334	14	0.95	0.01	0.92	0.97	533	27	0.87	0.01	0.85	0.89
	4	634	37	0.85	0.01	0.83	0.87	245	13	0.90	0.02	0.87	0.94	389	24	0.83	0.01	0.80	0.85
	5	451	21	0.82	0.01	0.80	0.85	169	9	0.87	0.02	0.83	0.90	282	12	0.80	0.02	0.77	0.83
	10	86	56	0.61	0.03	0.56	0.67	31	27	0.61	0.05	0.52	0.71	55	29	0.61	0.04	0.55	0.69

Figure 21: OS by tumour grade

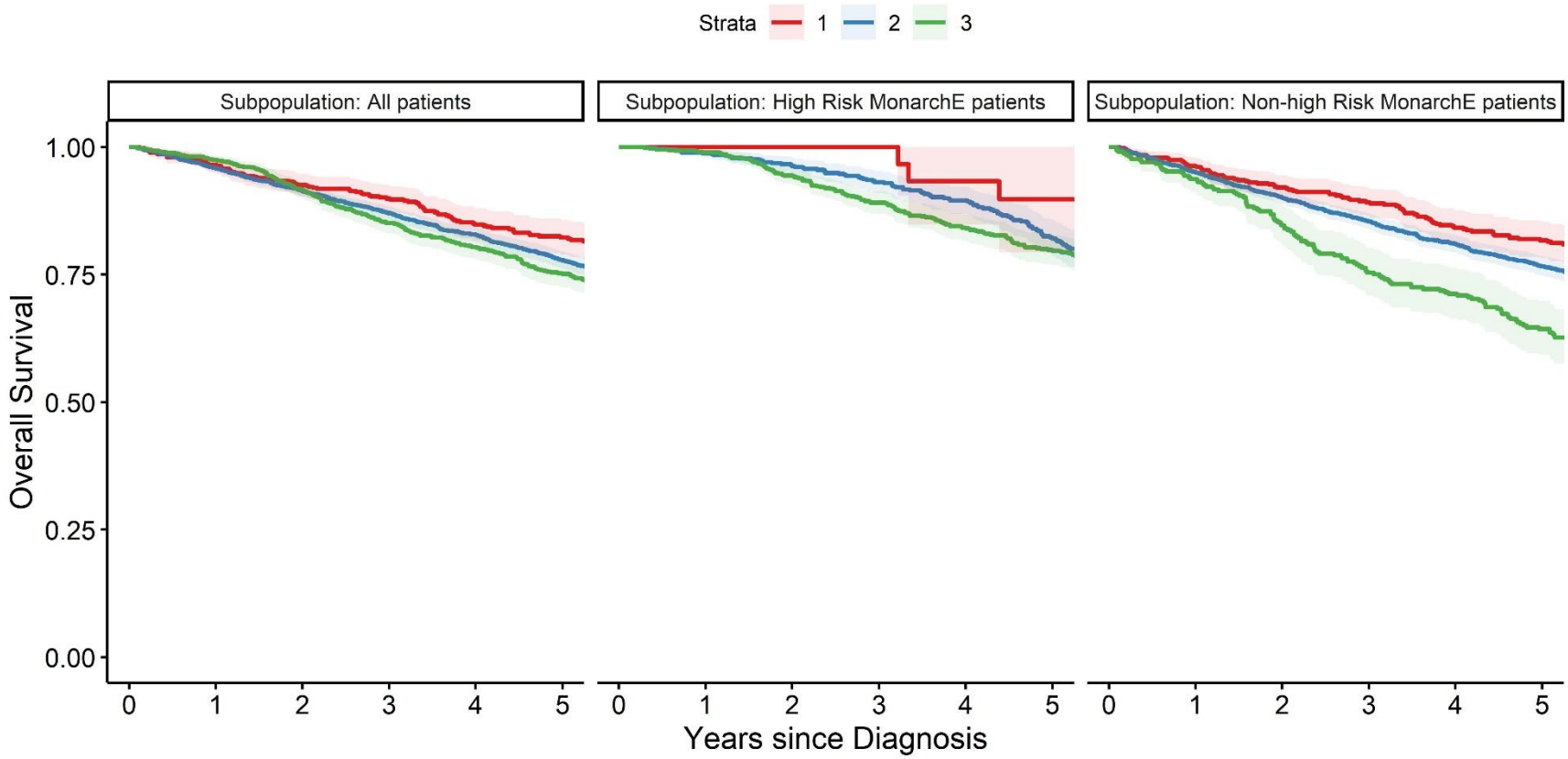


Table 23: OS by grade

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Grade	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
1	1	521	19	0.97	0.01	0.95	0.98	36	0	1.00	0.00	1.00	1.00	485	19	0.96	0.01	0.95	0.98
	2	473	21	0.93	0.01	0.90	0.95	35	0	1.00	0.00	1.00	1.00	438	21	0.92	0.01	0.90	0.94
	3	418	13	0.90	0.01	0.87	0.93	32	0	1.00	0.00	1.00	1.00	386	13	0.89	0.01	0.86	0.92
	4	375	23	0.85	0.02	0.82	0.88	28	2	0.93	0.05	0.85	1.00	347	21	0.84	0.02	0.81	0.88
	5	346	11	0.82	0.02	0.79	0.86	25	1	0.90	0.06	0.79	1.00	321	10	0.82	0.02	0.78	0.85
	10	166	56	0.66	0.02	0.61	0.71	<10	6	0.60	0.11	0.41	0.86	158	50	0.66	0.03	0.61	0.71
2	1	2594	113	0.96	0.00	0.95	0.97	565	7	0.99	0.00	0.98	1.00	2029	106	0.95	0.00	0.94	0.96
	2	2299	117	0.91	0.01	0.90	0.92	513	14	0.96	0.01	0.95	0.98	1786	103	0.90	0.01	0.89	0.91
	3	2042	106	0.87	0.01	0.86	0.88	455	16	0.93	0.01	0.91	0.95	1587	90	0.85	0.01	0.84	0.87
	4	1798	96	0.83	0.01	0.81	0.84	401	17	0.90	0.01	0.87	0.92	1397	79	0.81	0.01	0.79	0.83
	5	1566	105	0.78	0.01	0.76	0.79	336	32	0.82	0.02	0.79	0.86	1230	73	0.77	0.01	0.75	0.79
	10	709	265	0.61	0.01	0.59	0.63	130	64	0.61	0.03	0.56	0.67	579	201	0.61	0.01	0.58	0.63
3	1	1149	30	0.97	0.00	0.97	0.98	834	9	0.99	0.00	0.98	1.00	315	21	0.94	0.01	0.91	0.96
	2	1018	67	0.92	0.01	0.90	0.93	741	37	0.94	0.01	0.93	0.96	277	30	0.85	0.02	0.81	0.89
	3	880	70	0.85	0.01	0.83	0.87	641	40	0.89	0.01	0.87	0.91	239	30	0.75	0.02	0.71	0.80
	4	785	47	0.80	0.01	0.78	0.83	564	34	0.84	0.01	0.82	0.87	221	13	0.71	0.03	0.66	0.76
	5	688	49	0.75	0.01	0.73	0.78	495	28	0.80	0.01	0.77	0.83	193	21	0.64	0.03	0.59	0.70
	10	328	118	0.60	0.02	0.57	0.63	224	76	0.65	0.02	0.61	0.69	104	42	0.49	0.03	0.43	0.55
Unknown	1	52	9	0.85	0.04	0.77	0.95	<10	0	1.00	0.00	1.00	1.00	46	9	0.84	0.05	0.75	0.94
	2	47	4	0.79	0.05	0.69	0.90	<10	0	1.00	0.00	1.00	1.00	41	4	0.77	0.06	0.66	0.89
	3	37	9	0.64	0.06	0.53	0.77	<10	<10	0.83	0.15	0.58	1.00	32	8	0.62	0.07	0.50	0.76
	4	32	5	0.55	0.06	0.44	0.69	<10	<10	0.67	0.19	0.38	1.00	28	4	0.54	0.07	0.42	0.69
	5	29	3	0.50	0.06	0.39	0.64	<10	<10	0.67	0.19	0.38	1.00	25	3	0.48	0.07	0.36	0.64
	10	16	7	0.37	0.06	0.26	0.52	<10	<10	0.50	0.20	0.22	1.00	13	6	0.36	0.07	0.25	0.52

Figure 22: OS by age group

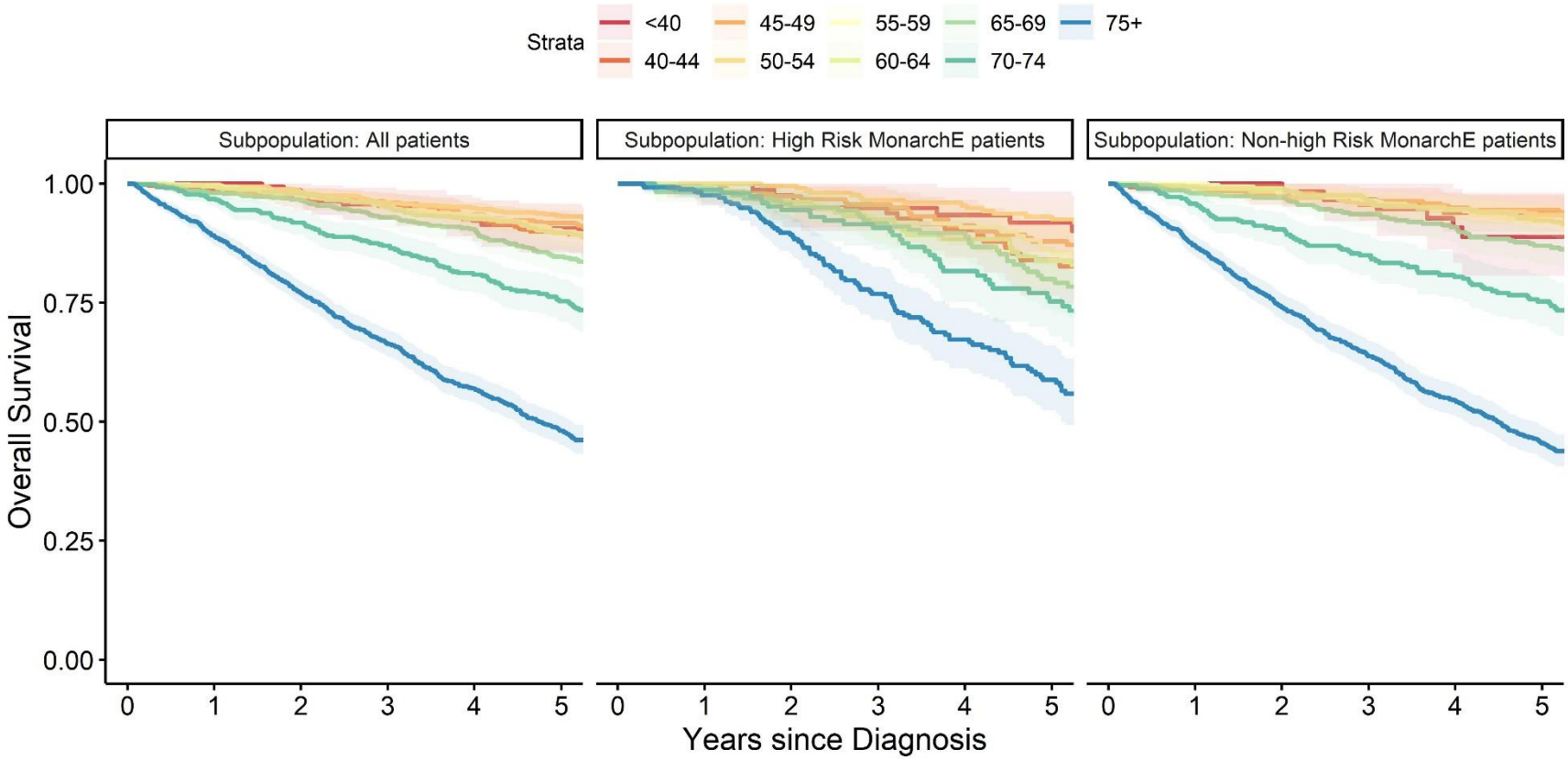


Table 24: OS by age group

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Age	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
<40	1	149	0	1.00	0.00	1.00	1.00	81	0	1.00	0.00	1.00	1.00	68	0	1.00	0.00	1.00	1.00
	2	136	2	0.99	0.01	0.97	1.00	76	2	0.97	0.02	0.94	1.00	60	0	1.00	0.00	1.00	1.00
	3	117	4	0.96	0.02	0.92	0.99	66	2	0.95	0.03	0.90	1.00	51	2	0.97	0.02	0.92	1.00
	4	108	4	0.92	0.02	0.88	0.97	62	1	0.93	0.03	0.88	0.99	46	3	0.91	0.04	0.83	0.99
	5	98	2	0.91	0.03	0.86	0.96	55	1	0.92	0.03	0.86	0.98	43	1	0.89	0.04	0.81	0.98
	10	47	11	0.78	0.04	0.71	0.87	22	7	0.78	0.05	0.68	0.90	25	4	0.79	0.06	0.68	0.92
40-44	1	246	3	0.99	0.01	0.97	1.00	100	2	0.98	0.01	0.95	1.00	146	1	0.99	0.01	0.98	1.00
	2	225	5	0.97	0.01	0.94	0.99	89	3	0.95	0.02	0.91	0.99	136	2	0.98	0.01	0.96	1.00
	3	203	3	0.95	0.01	0.93	0.98	81	0	0.95	0.02	0.91	0.99	122	3	0.96	0.02	0.92	0.99
	4	190	6	0.92	0.02	0.89	0.96	76	4	0.90	0.03	0.84	0.97	114	2	0.94	0.02	0.90	0.98
	5	167	5	0.90	0.02	0.86	0.94	64	5	0.84	0.04	0.76	0.92	103	0	0.94	0.02	0.90	0.98
	10	91	21	0.76	0.03	0.70	0.83	27	14	0.63	0.06	0.52	0.75	64	7	0.86	0.03	0.79	0.93
45-49	1	440	1	1.00	0.00	0.99	1.00	188	0	1.00	0.00	1.00	1.00	252	1	1.00	0.00	0.99	1.00
	2	409	9	0.98	0.01	0.96	0.99	174	5	0.97	0.01	0.95	1.00	235	4	0.98	0.01	0.96	1.00
	3	380	7	0.96	0.01	0.94	0.98	158	3	0.96	0.02	0.93	0.99	222	4	0.96	0.01	0.94	0.99
	4	346	10	0.93	0.01	0.91	0.96	140	7	0.91	0.02	0.87	0.96	206	3	0.95	0.01	0.92	0.98
	5	316	6	0.92	0.01	0.89	0.94	121	5	0.88	0.03	0.83	0.93	195	1	0.94	0.01	0.92	0.97
	10	170	26	0.83	0.02	0.78	0.87	60	9	0.80	0.03	0.73	0.87	110	17	0.84	0.03	0.79	0.90
50-54	1	576	3	0.99	0.00	0.99	1.00	225	0	1.00	0.00	1.00	1.00	351	3	0.99	0.00	0.98	1.00
	2	526	7	0.98	0.01	0.97	0.99	206	1	1.00	0.00	0.99	1.00	320	6	0.97	0.01	0.96	0.99
	3	478	11	0.96	0.01	0.94	0.98	183	6	0.97	0.01	0.94	0.99	295	5	0.96	0.01	0.94	0.98
	4	437	6	0.95	0.01	0.93	0.97	166	2	0.95	0.01	0.93	0.98	271	4	0.94	0.01	0.92	0.97
	5	404	8	0.93	0.01	0.91	0.95	151	5	0.92	0.02	0.89	0.96	253	3	0.93	0.01	0.91	0.96
	10	202	28	0.84	0.02	0.81	0.88	64	16	0.79	0.04	0.72	0.86	138	12	0.88	0.02	0.84	0.92

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Age	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
55-59	1	466	2	1.00	0.00	0.99	1.00	154	2	0.99	0.01	0.97	1.00	312	0	1.00	0.00	1.00	1.00
	2	415	10	0.97	0.01	0.96	0.99	135	5	0.95	0.02	0.92	0.99	280	5	0.98	0.01	0.97	1.00
	3	377	9	0.95	0.01	0.93	0.97	120	4	0.92	0.02	0.88	0.97	257	5	0.97	0.01	0.94	0.99
	4	342	7	0.93	0.01	0.91	0.96	108	2	0.91	0.02	0.86	0.96	234	5	0.95	0.01	0.92	0.97
	5	308	11	0.90	0.02	0.87	0.93	94	5	0.86	0.03	0.81	0.92	214	6	0.92	0.02	0.89	0.95
	10	164	28	0.80	0.02	0.75	0.84	45	9	0.76	0.04	0.68	0.85	119	19	0.82	0.03	0.77	0.87
60-64	1	450	3	0.99	0.00	0.99	1.00	155	1	0.99	0.01	0.98	1.00	295	2	0.99	0.00	0.98	1.00
	2	419	6	0.98	0.01	0.97	0.99	137	5	0.96	0.02	0.93	0.99	282	1	0.99	0.01	0.98	1.00
	3	382	12	0.95	0.01	0.93	0.97	116	5	0.92	0.02	0.88	0.97	266	7	0.97	0.01	0.94	0.99
	4	348	10	0.93	0.01	0.90	0.95	102	5	0.88	0.03	0.83	0.94	246	5	0.95	0.01	0.92	0.97
	5	321	11	0.90	0.02	0.87	0.93	90	5	0.84	0.03	0.78	0.90	231	6	0.92	0.02	0.89	0.96
	10	173	39	0.76	0.02	0.71	0.81	39	13	0.67	0.05	0.58	0.78	134	26	0.80	0.03	0.75	0.85
65-69	1	494	10	0.98	0.01	0.97	0.99	159	3	0.98	0.01	0.96	1.00	335	7	0.98	0.01	0.97	0.99
	2	461	8	0.96	0.01	0.95	0.98	148	5	0.95	0.02	0.92	0.98	313	3	0.97	0.01	0.95	0.99
	3	416	16	0.93	0.01	0.91	0.95	134	5	0.92	0.02	0.87	0.96	282	11	0.94	0.01	0.91	0.96
	4	384	11	0.90	0.01	0.88	0.93	125	3	0.90	0.02	0.85	0.95	259	8	0.91	0.02	0.88	0.94
	5	340	24	0.85	0.02	0.81	0.88	103	13	0.80	0.03	0.74	0.87	237	11	0.87	0.02	0.83	0.91
	10	165	44	0.70	0.02	0.65	0.75	54	17	0.64	0.04	0.56	0.73	111	27	0.73	0.03	0.67	0.79
70-74	1	418	14	0.97	0.01	0.95	0.98	149	2	0.99	0.01	0.97	1.00	269	12	0.96	0.01	0.93	0.98
	2	369	21	0.92	0.01	0.89	0.94	129	6	0.94	0.02	0.91	0.98	240	15	0.90	0.02	0.87	0.94
	3	325	19	0.87	0.02	0.84	0.90	115	5	0.91	0.02	0.86	0.96	210	14	0.85	0.02	0.81	0.89
	4	284	22	0.81	0.02	0.77	0.85	92	11	0.82	0.03	0.75	0.89	192	11	0.80	0.02	0.76	0.85
	5	246	19	0.75	0.02	0.71	0.80	81	7	0.75	0.04	0.68	0.83	165	12	0.75	0.03	0.70	0.81
	10	106	53	0.55	0.03	0.50	0.61	30	21	0.51	0.05	0.42	0.62	76	32	0.57	0.03	0.51	0.65

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Age	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
75+	1	1077	135	0.89	0.01	0.87	0.91	230	6	0.97	0.01	0.96	0.99	847	129	0.87	0.01	0.85	0.89
	2	877	141	0.77	0.01	0.75	0.79	201	19	0.89	0.02	0.85	0.93	676	122	0.74	0.01	0.71	0.77
	3	699	117	0.66	0.01	0.64	0.69	160	27	0.77	0.03	0.71	0.83	539	90	0.64	0.02	0.61	0.67
	4	551	95	0.57	0.01	0.54	0.60	126	19	0.67	0.03	0.61	0.74	425	76	0.54	0.02	0.51	0.58
	5	429	82	0.48	0.02	0.45	0.51	101	15	0.59	0.03	0.52	0.66	328	67	0.45	0.02	0.42	0.49
	10	101	196	0.21	0.02	0.18	0.24	24	41	0.28	0.04	0.21	0.37	77	155	0.19	0.02	0.16	0.23

Figure 23: OS by inflammatory disease

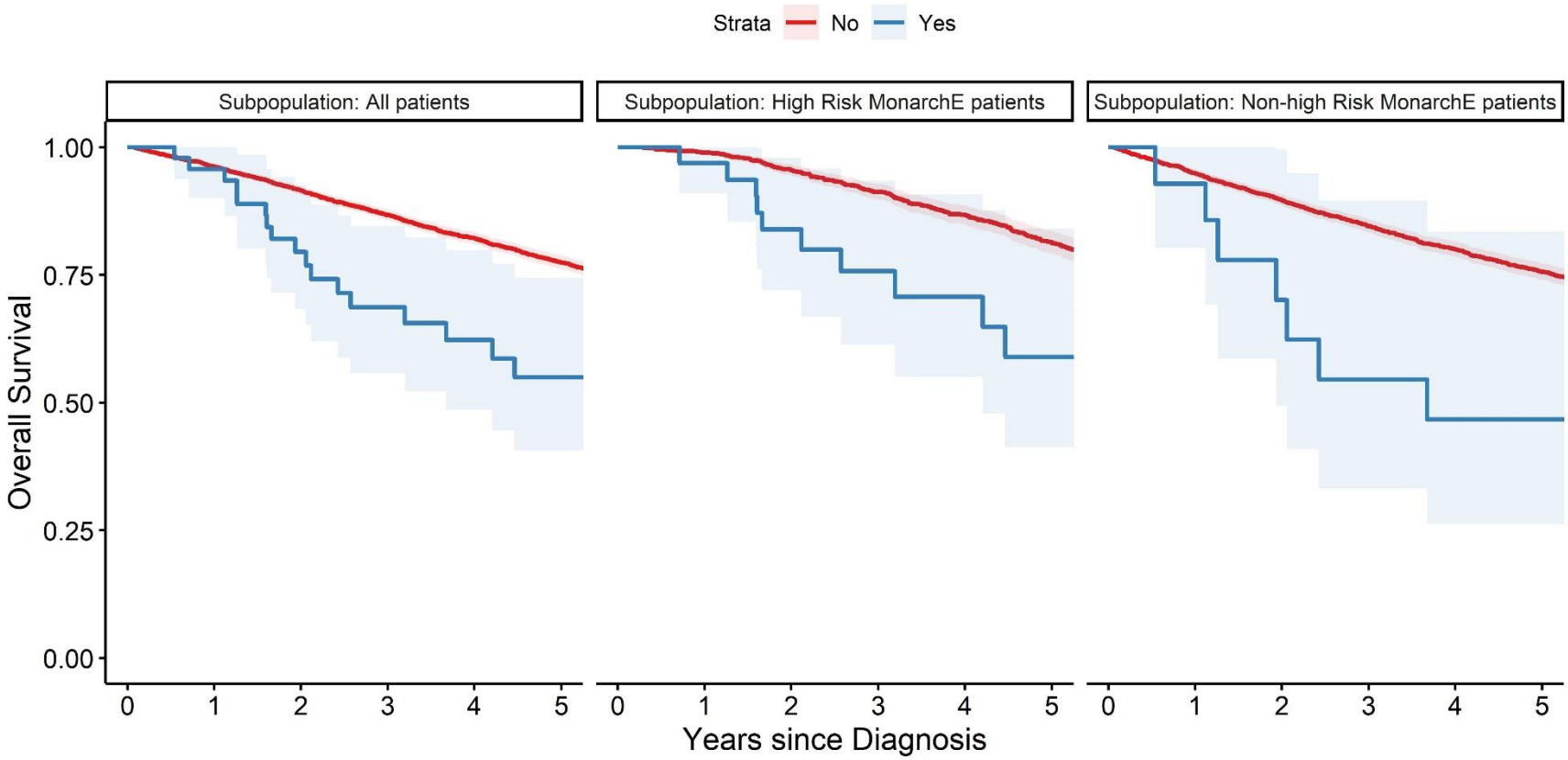


Table 25: OS by inflammatory disease status

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Inflam	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
No	1	4272	169	0.96	0.00	0.96	0.97	1410	15	0.99	0.00	0.98	0.99	2862	154	0.95	0.00	0.94	0.96
	2	3806	202	0.92	0.00	0.91	0.92	1273	47	0.96	0.01	0.94	0.97	2533	155	0.90	0.01	0.89	0.91
	3	3355	194	0.87	0.01	0.86	0.88	1118	55	0.91	0.01	0.90	0.93	2237	139	0.85	0.01	0.83	0.86
	4	2971	169	0.82	0.01	0.81	0.83	984	53	0.87	0.01	0.85	0.89	1987	116	0.80	0.01	0.79	0.82
	5	2615	166	0.77	0.01	0.76	0.79	850	59	0.81	0.01	0.79	0.84	1765	107	0.76	0.01	0.74	0.77
	10	1214	444	0.61	0.01	0.59	0.63	363	146	0.64	0.02	0.61	0.67	851	298	0.60	0.01	0.58	0.62
Yes	1	44	2	0.96	0.03	0.90	1.00	31	1	0.97	0.03	0.91	1.00	13	1	0.93	0.07	0.80	1.00
	2	31	7	0.80	0.06	0.68	0.92	22	4	0.84	0.07	0.72	0.98	<10	<10	0.70	0.13	0.49	1.00
	3	22	4	0.69	0.07	0.56	0.85	15	2	0.76	0.08	0.61	0.93	<10	<10	0.55	0.14	0.33	0.90
	4	19	2	0.62	0.08	0.49	0.80	13	1	0.71	0.09	0.55	0.91	<10	<10	0.47	0.14	0.26	0.84
	5	14	2	0.55	0.08	0.41	0.74	10	2	0.59	0.11	0.41	0.84	<10	<10	0.47	0.14	0.26	0.84
	10	<10	<10	0.45	0.09	0.30	0.68	<10	<10	0.52	0.11	0.34	0.80	<10	<10	0.35	0.14	0.16	0.79

Figure 24: OS by pre vs post COVID-19 pandemic

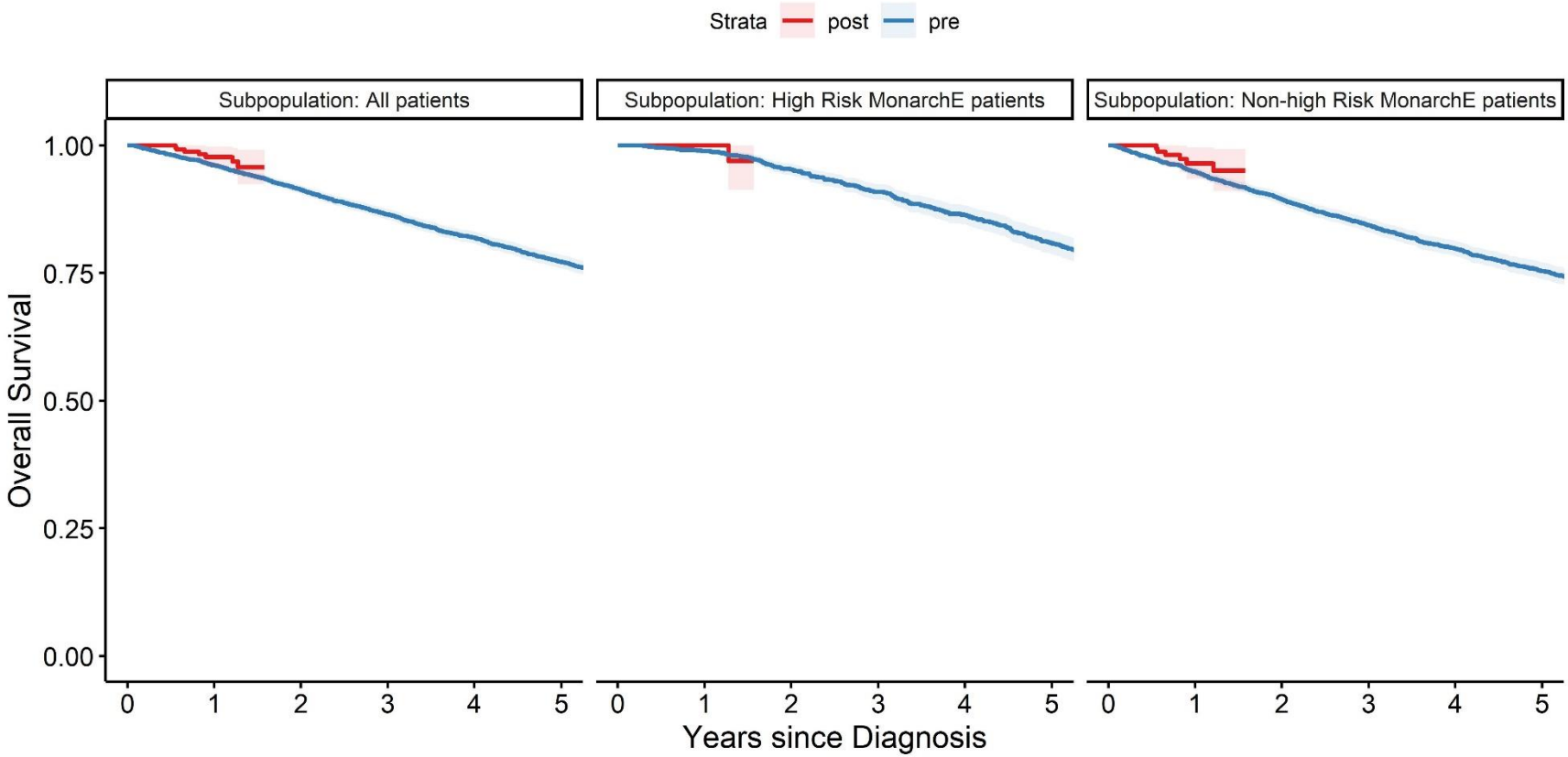


Table 26: OS by pre vs post COVID pandemic

OS		All patients						High risk MonarchE patients						Non-high risk MonarchE patients					
Covid-19 Pandemic	Years	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper	n.risk	n.event	surv	std.err	lower	upper
Post	1	156	5	0.98	0.01	0.96	1.00	55	0	1.00	0.00	1.00	1.00	101	5	0.96	0.02	0.93	1.00
Pre	1	4160	166	0.96	0.00	0.96	0.97	1386	16	0.99	0.00	0.98	0.99	2774	150	0.95	0.00	0.94	0.96
	2	3837	207	0.91	0.00	0.91	0.92	1295	50	0.95	0.01	0.94	0.96	2542	157	0.89	0.01	0.88	0.91
	3	3377	198	0.86	0.01	0.85	0.88	1133	57	0.91	0.01	0.89	0.92	2244	141	0.84	0.01	0.83	0.86
	4	2990	171	0.82	0.01	0.81	0.83	997	54	0.86	0.01	0.85	0.88	1993	117	0.80	0.01	0.78	0.81
	5	2629	168	0.77	0.01	0.76	0.79	860	61	0.81	0.01	0.79	0.83	1769	107	0.75	0.01	0.74	0.77
	10	1219	446	0.61	0.01	0.59	0.63	365	147	0.63	0.02	0.60	0.67	854	299	0.60	0.01	0.58	0.62

6.4 Adverse events/adverse reactions

N/A

7. Discussion

7.1 Key results

The monarchE trial recently showed that the combination of adjuvant abemaciclib with endocrine therapy in HR+, HER2-, high-risk early breast cancer demonstrated clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse free survival (DRFS) (14). Here, we report the real world experience from 4600 patient records treated for early breast cancer by a tertiary referral cancer centre, over a fifteen year period, with a median follow up of just under 7 years. The primary objective of the study was to describe the clinical characteristics of patients with early breast cancer by high risk (HRisk) and non-high risk (non-HRisk) according to the monarchE criteria. This is the second presentation of a real world cohort aligned with this definition. Sheffield et al 2021 ASCO (15) reported a similar retrospective review of the US based Flatiron electronic health record database between 2011-2020, using clinical pathological features to identify High Risk patients from all stage I-III HR+, HER2- Breast cancer. High risk was defined as (≥ 4 positive axillary lymph nodes (LN), or 1-3 positive axillary LN and ≥ 1 of the following: Grade 3, tumor size ≥ 5 cm, or Ki-67 ≥ 20%) and 'low risk (LoR) group' (pts who do not meet above criteria, including a subset with node negative (N0) disease. They identified 13.8% as high risk, and 86.2% as low risk. 76.6% were postmenopausal and median age was 64 years. Of the 557 high risk patients 41.5% had greater than or equal to 4 positive lymph nodes,and 1-3 had positive axillary lymph nodes with an additional factor. Recurrence in this group was measured as a 2 year DRFS of 88.1%.

Two results in our study were unexpected: the secondary objectives of survival (IDFS and OS) and menopausal status. Unexpectedly IDFS and OS appeared to be better in the HRisk group compared to the non-HRisk group (IDFS figure 5, table 7 and OS figure 6, table 8) which is an incongruent finding to Sheffield el al (15). Similarly, there is a further unexpected finding regarding menopausal status; IDFS and OS in postmenopausal patients were worse than in pre and perimenopausal patients (IDFS figure 7 and OS figure 17). It is difficult to explain these findings without further regression-based analysis to adjust for casemix factors. Missing data occurred predominantly in the non-HRisk group, which was by nature a group defined by exclusion of the high-risk criteria rather than by inclusion of low risk criteria. Additional high risk features not captured in the documented characteristics may explain this difference as a consequence of the study design. This may have inadvertently resulted in the inclusion of some patients with high risk factors within the non-HRisk group and we suggest this has influenced the survival outcomes. For the non-high risk group who were defined by exclusion, further research is required to characterise this important population of early breast cancer patients in more detail. An additional analysis that defines a non-high risk group by specific inclusion criteria is recommended.

It is also possible that factors we have not captured here, such as Ki67 level which is not routinely tested in the UK, but is a recognized prognostic factors in early breast cancer, may have affected results. Other population factors which we have not studied here, such as diet, may also have some effect on the finding.

Given one of the major limitations of the study is completeness of data capture for our objectives of interest, where possible we focus upon the most complete results for the cohorts of high risk patients, non-HRisk group and total population.

Secondary objectives of the study were to describe treatment patterns, frequency of genomic testing, healthcare resource utilization and estimates of survival without recurrence in the total, HRisk and non-HRisk populations, and for subgroups of interest at pre-specified follow up.

Demographics

4600 patient records were included in our study. 1498 (32.6%) patients had monarchE HRisk characteristics, the remaining 3102 (67.4%) were considered non-high risk by monarchE inclusion criteria. 99.3% were female, male patients were distributed proportionally between the high and non-HRisk groups. In the total population only 3.4% of patients were under 40 years of age. 31.6% of patients were under the age of 54 years.

A high proportion of the overall population were aged over 70 years (36.8%), which is higher than the 25-30% rate seen in developed countries in women over the age of 70years (16). Patients in the HRisk group were generally younger with relatively fewer comorbidities, 16.2%, aged over 75 years, compared to 32.3% in the non-HRisk group. In the survival analyses we saw an IDFS and OS trend that outcomes worsened with increasing age, and particularly in the over 75 years age group which was worse across both subgroups. The cause of this may be multifactorial. Whilst tumours are generally more indolent in the elderly, the entire range of aggressiveness can be seen. A variety of problems are associated with increasing age and cancer treatment. Older patients are less likely to be treated according to accepted treatment guidelines and undertreatment can have a consequent negative effect upon survival. Compliance to anticancer treatments including endocrine therapy is an issue as the elderly are more prone to adverse effects and can be more sensitive to them, something we did not measure within this study.

Charlson Comorbidity Index data was available but is limited by data completeness (26% in the HRisk group unavailable). The majority of patients in both groups had a CCI of 0.

In this study a clear relationship was demonstrated between increasing Comborbidity index and poorer outcomes for both IDFS and OS (figures 6 and 15). Comorbidity in breast cancer is common with 20-35% of patients having at least one. The presence of comorbidities influences treatment decisions, treatment completion and therefore outcomes. Patients with comorbidity may also experience delayed diagnosis, sub optimal treatment and increased postoperative complications (17, 18). A recent systematic review, Salas et al 2021, of the use of comorbidity indices in patients with cancer, including of breast cancer, confirms the association between comorbidity burden and decreased survival that we have seen (19). 33 of 39 studies included in this systematic review used the CCI, and thus the authors conclude a CCI-based index should be strongly considered in breast cancer studies, despite a lack of robust reviews or metanalyses for its use in breast cancer.

78.5% of patients in the total population were postmenopausal; 21.5% were pre or perimenopausal. In the HRisk group 71.5% were postmenopausal and 28.5% were pre or peri-menopausal compared to 81.9% and 18.1% in the non-HRisk group respectively. In this study, HRisk group patients tended to be proportionally younger, and with higher pre and perimenopausal status compared to the non-HR group. As previously mentioned we note a surprising subgroup result for menopausal status with post-menopausal status associated with poorer IDFS and OS outcomes (figures 7 and 17).

Diagnosis and surgery characteristics:

The most complete data was available for staging using the AJCC system. In the HRisk group 3.1% and non-HRisk group 8.3% of data was unavailable. Staging by the AJCC system showed less stage 1 disease and more stage 2 and 3A-C in the HRisk group respectively 14.3%, 62.3%, 20.3%, compared to the non-HR group 37.8%,43.3%, 10.6%.

In the total population who did not receive neoadjuvant therapy, pathological tumour and nodal status was also available, however completeness is limited by a high proportion of missing data in the non-HRisk group, wherein 43.7% of nodal data and 35.8% of tumour size data is unavailable. In the HRisk group T1 tumours constituted 22.8%, T2 47.9%, and T3 tumours 27.6%, missing data 1.7%. In the nonHR group there were more T1 tumours (38.1%), less T2 (24.8%) and most markedly less T3 tumours (1.4%). Because of the high level of aforementioned missing data the following comparison should be interpreted with caution. In the secondary objective subgroup survival analysis there was a clear relationship between increasing tumour size (figure 9 and 18) and worse survival outcomes in IDFS and OS across risk groups. The HRisk outcomes were poorer than non-HRisk, and poorest outcomes are more marked in the non-HR patients with T3 stage tumours >50mm.

The relationship with increasing burden of nodal disease was also clearly demonstrated in the survival analyses. In the HR group N0 disease was impossible as patients required >1 positive lymph nodes for inclusion as per the study criteria. In the HRisk group N1 disease constituted 47.9%, N2 34.9% and N3 17.2%. Both IDFS and OS outcomes were similar for patients with N1 (1-3 Lymph nodes) and N2 (4-9 lymph nodes), however N3 (10+ lymph nodes) demonstrated much worse outcomes, figures 8 and 17.

Grade and inflammatory

Subgroup analysis demonstrates that increasing tumour grade is associated with worse IDFS and OS outcomes across both populations (figures 11 and 20). Table 23 OS by grade provides absolute numbers, and we can see that in the HRisk group there are :

- Grade 1 – 36
- Grade 2 – 565
- Grade 3 – 834
- Unknown <10

As this is a real world data set, we felt it was important to include inflammatory breast cancers which would be excluded from many clinical trials due to poorer outcomes. Absolute numbers of inflammatory breast cancer were low with 30 patients in the HRisk group, and 12 patients in the non-HRisk group. The presence of Inflammatory breast cancer was linked to worse survival outcomes (figures 13 and 22).

Gene expression profiling and HR status

Greater than 99.8% of tumours were ER positive, <0.2% ERnegative but by definition must have been PR positive as we allowed HR+ patients within the inclusion criteria. PR positivity was 33.6% in the total population and similarly distributed across HRisk and non-HRisk groups. In the secondary subgroup analysis of survival PR negativity correlated with worsening outcomes (figures 10 and 19).

Treatments

Chemotherapy

Neo-Adjuvant Chemotherapy was received by 15.6% of the HRisk population and adjuvant by 65.8%. 31.4% of data was unavailable in the HRisk, and 74.8% in the non-HRisk populations. In the non-HRisk group this compares to neoadjuvant chemotherapy given in 6.5% and adjuvant chemotherapy in 25.2%. We are relatively confident that this data truly represents the decision to give chemotherapy as the percentage of patients receiving chemotherapy is consistent with what would be expected, and the level of accuracy from the Chemocare system is very high. Unavailable data in this instance represents the decision not to give chemotherapy.

Patients could have received both neo and adjuvant chemotherapy treatment. In the adjuvant setting combination anthracycline and taxane based chemotherapy regimens were most used. In the neoadjuvant setting other therapies were used most.

Table 2728: Type of Chemotherapy received in patients described as HRisk

	Neoadjuvant %	Adjuvant %
Anthracycline and taxane	38.9	55.9
Taxane	7.2	15.9
Anthracycline	13.9	15.7
Other (not containing anthracycline or taxane)	39.9	12.4

Endocrine therapy

High levels of missing data of endocrine treatment limit interpretation of this data. In the premenopausal patients (all N=998, HRisk=427, non-HRisk= 571) tamoxifen was used in approximately 50% of patients regardless of risk status; similarly NSAIs were used in 11.8-16.3% across the groups; steroidal AI in 0-<2.5%. In postmenopausal patients again regardless of risk, as might be expected we see a reverse trend with tamoxifen used in 5.5-11.2% and NSAIs used in 50.9-56.4% i.e. the majority of patients. Ovarian Function Suppression (OFS) data is grossly incomplete with 95.2% of the total population data not available. Despite this major limitation, goserelin was given exclusively in 8.3% of the HR group, compared to non-HR and total populations (3.1% and 4.8%). Following publication of a number of major trials (e.g. SOFT, TEXT) it is more commonplace now to consider the use of OFS with Aromatase inhibitor for pre-menopausal patients deemed at high clinical risk of recurrence. We have not seen this practice even within the HRisk population of this study, instead we have seen a preponderance for tamoxifen prescription. However the study includes patients treated over for a fifteen year timeframe, and so this may not be representative of current clinical practice.

Radiotherapy

Radiotherapy was received by more patients in the HRisk group 92.1%, than in the non-HR group 63.3%. Breast radiation after breast conserving surgery should be considered, but in low risk tumours or where life expectancy is short the absolute benefit may be very limited.

Timelines

We also looked at time from first diagnosis to chemotherapy, surgery and radiotherapy. There were slight differences between the HRisk and non-HRisk populations. Median time from diagnosis to surgery was 71.2 weeks in the non-HR group and approximately 16 weeks longer in the HRisk group, this may be explained by higher proportions of patients receiving neoadjuvant chemotherapy. Similarly, time from

diagnosis to radiotherapy was 137.95 days in the non-HRisk group and 214.95 days in the HRisk group which we suggest is due to higher proportions of patients receiving (neo)adjuvant chemotherapy.

Healthcare utilisation

Mean number of outpatient visits per patient was higher in the HRisk group at 7.1, and lower in the non-HR group which we suggest is likely due to the higher numbers of appointments associated with receiving chemotherapy and radiotherapy. Mean number of inpatient admissions per patient was 2 (range 0-23) with a mean duration of 6.6 days. This was similar across HRisk and non-HRisk populations.

Cancer Recurrence and survival

A secondary outcome analysis of the study looked at absolute numbers of recurrence and the survival measures of IDFS and OS. 1684 patients in the study had coded IDFS events; 489 occurred in the HRisk group and 1195 in the non-HRisk. IDFS is a composite endpoint, defined as occurrence of any of the following: ipsilateral invasive breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or second non-breast invasive cancer. Note: In-situ events are not included.

381 of 4600 patients in the total population experienced a coded recurrence; similar numbers of events, 196 occurring in the HRisk, and 185 in the non-HRisk. Time from diagnosis to cancer recurrence was over a year shorter in the HRisk group at 33.9 months, compared to 46.6 months in the non-HRisk group.

The time from surgery to an IDFS event was shorter in the HRisk group at 45.1 months compared to 60.3 months in the non-HRisk group.

In the monarchE study reported by Harbeck et al 2021, abemaciclib plus endocrine therapy resulted in a 3 years IDFS rate of 88.8%, compared to the AET only arm of 83.4% (14). The non-HRisk group in this study performs similarly, if not slightly worse, to the placebo arm of monarchE with a 3 year IDFS rate of 82%. However the HRisk group in this study does not perform as expected (see figure 5) with a much better than expected IDFS rate of 87%. Similarly in the overall survival analysis the HRisk group had a better outcome than the non-HRisk (figure 6).

Overall the study population performs significantly worse than would be expected in comparison to the medical literature (20) when looking at both high and non-HRisk groups. At 10 years follow up, the OS rate demonstrates a mere 63% overall survival in the HRisk and 60% overall survival in the non-HRisk groups (table 8). For example, in the EBCTCG meta analysis of adjuvant tamoxifen versus aromatase inhibitors for postmenopausal women ten year mortality from deaths due to any cause ranged from 21-24%.

1520 patients have died at the time of our analysis, of which 435 occurred in the HRisk, and 1085 in the non-HRisk group. Also incongruent with what would be expected, time from diagnosis to death was higher at 56.1 months in the HRisk group, compared to 44.5months in the non-HRisk group. As noted previously these are surprising findings. We suspect that large numbers of missing data which occurred predominantly in the non-HRisk group may have inadvertently resulted in the inclusion of some patients with high risk factors within the non-HRisk group. We suggest this has influenced the survival outcomes. It is also possible that intrinsic breast cancer and population related factors may have had an effect here. In terms of the measures themselves, we did not measure breast cancer specific overall survival and cannot exclude the chance of higher numbers of non-breast cancer related deaths contributing to the large numbers of deaths seen. The IDFS composite endpoint includes deaths due to any cause, a flaw of our data is that we have not captured cause of death.

7.2 Limitations

This is the second study to identify a population in the real world aligned with the criteria for inclusion within the high risk monarchE study.

We included patients with HR+, HER2- stage I-III EBC with nodal involvement. The definition of HR+ in our study included patients with ER or PR scores of greater than or equal to 3, which are sometimes referred to as ‘ low ‘ER/PR’. The high risk population in our study is aligned to inclusion criteria for the majority of patients (~91%) in monarchE which are:

- > 4 ipsilateral Lymph nodes on pathological staging OR
- Pathological tumour involvement in 1-3 ipsilateral axillary lymph nodes AND at least one of the following criteria:
    - Grade 3
    - Pathological primary tumour size > 5 cm, or for patients receiving neoadjuvant therapy tumour size >5 cm on breast imaging.

Within the population studied (n=4600), approximately one third of patients (n=1498) were classified as HRisk by the above definition. If all Stage 1-3C patients were included in the total population, including node negative patients, this proportion would obviously be less. The data from this tertiary referral unit clearly demonstrates a significant proportion of high risk patients amongst node positive, HR+, HER2- early breast cancer populations, with a significant unmet need in terms of their overall prognosis.

In recent years standards of care have changed in terms of type and duration of adjuvant endocrine therapy and the use of bisphosphonates. We saw tamoxifen most commonly used regardless of risk status in premenopausal patients within this study as an example, when evidence now suggests the combination or AI with OFS is more efficacious in HRisk pre menopausal patients. It is perhaps too soon to see the affects on this study population, but looking ahead in the medium term collection of this data and associated outcomes is of interest. For the non-HRisk group who have been discussed at length here, and that were defined by exclusion, further research is required to characterise this important population of early breast cancer patients in more detail. Areas of interest include the impact of age and comorbidity.

In order to minimise the effect or bias from clinical trial participants within this study, exclusion of patients from the monarchE trial was applied. The study site did not participate in other major adjuvant CDK4/6i trials.

Real world data is observed from routine clinical practice and hence missing data, as in all real world studies, is a limitation of this study; here the missing data may have confounded some key results. Counterpoint to this, one advantage of the data utilised was the linkage of six well established data sources including a population based registry and treatment databases to indirectly validate observations, and the use of an individualised patient number to perform data linkage. Expansion of the data set to a national level would certainly provide more data, however the same issues we experienced in terms of data availability would need to be addressed. Also, improving clarity of definitions and collecting more in depth information could inform the results, for example the use of breast cancer specific mortality rather than overall mortality would be very interesting, and may give some direction as to population based factors currently unaccounted for. Our objective here was to describe the clinical features and outcomes in this population. We cannot infer which single or combinations of prognostic factors, for example, grade, tumour size, axillary burden, were the drivers behind the outcomes seen and further study in this area would be interesting.

7.3 Interpretation

As a real world cohort, the described patient characteristics, outcomes and treatments should be taken at face value. The nature of real world data is that not all variables can be ascertained but including these patient in the results promotes representativeness and will allow best representation the data to inform the Health Technology Assessment process.

7.4 Generalisability

The population studied represents that of routine clinical practice in the Lothian region of Scotland and is primarily urban in nature. Practice is aligned to that of the United Kingdom, and thus results should be generalizable to similarly developed areas in other countries. Differences between our study and the results of highly selected trials populations are to be expected, and we hope the study findings will augment the findings of such randomized controlled trials.

8. Other information

N/A

9. Conclusions

- Real world data from a tertiary referral unit in the Lothian region of Scotland confirm that a considerable proportion, approximately one third of the population studied (n=4600), of HR+, HER2− node positive EBC represents HRisk disease.
- This population had associated poor survival outcomes, at 10 years follow up the OS rate was 63% in the HRisk, and 60% overall survival in the non-HRisk groups. This points to an unmet need in the study population and highlights the need for improved treatments.
- In the HRisk group, 16% received neoadjuvant chemotherapy, 66% adjuvant chemotherapy and 92% radiotherapy; AET mostly involved letrozole (34%).
- Health care utility was higher in the HRisk group with higher numbers of outpatient attendences.
- The relationship between increasing burden of nodal disease, grade and tumour size with IDFS and OS was also clearly demonstrated in the survival analyses.
- Two unanticipated results were seen:
    - Secondary objectives of survival (IDFS and OS) in the HRisk group compared to the non-HRisk group
    - Menopausal status
- For the non-HRisk group, which was defined by exclusion, further research is required to characterise this important population of early breast cancer patients in more detail. Areas of interest include the impact of age and comorbidity.
- This population studied represents that of routine clinical practice in a primarily urban setting, where practice aligns to that of the United Kingdom as a whole. Thus results should be generalizable to other developed countries. Differences between our study and the results of highly selected RCTs are to be expected, and we hope the study findings will augment the findings of these trials in the real world setting.

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Appendix

Figure A: 10-year Overall Survival – High Risk MonarchE patients

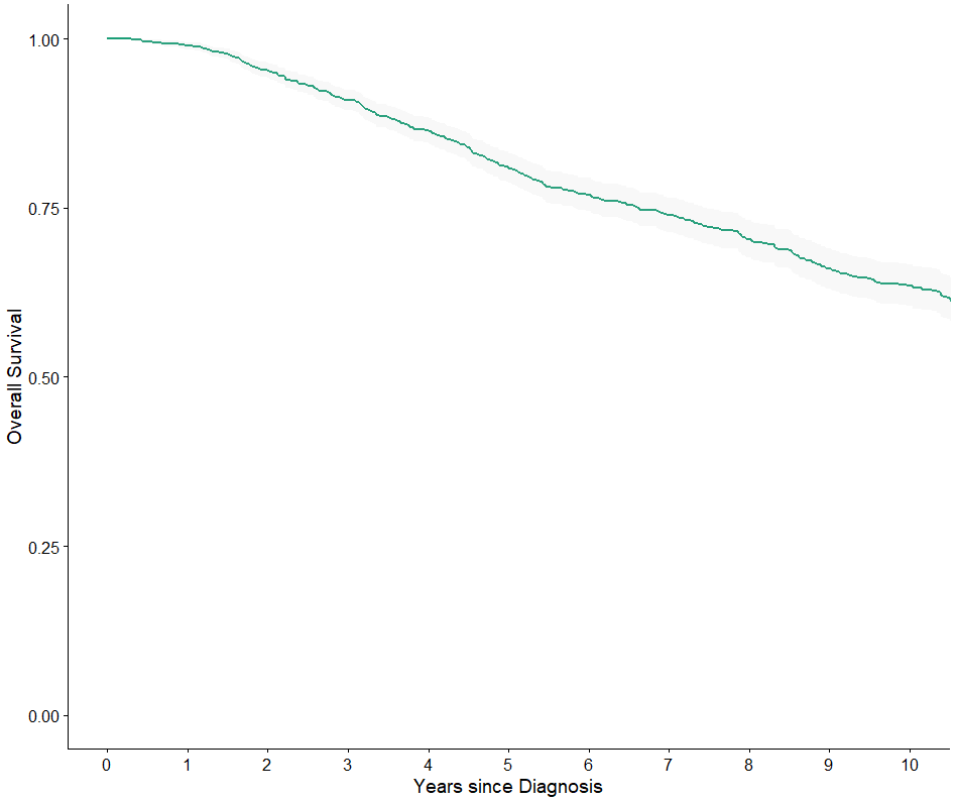


Figure B: 10-year Invasive Disease-free Survival – High Risk MonarchE patients

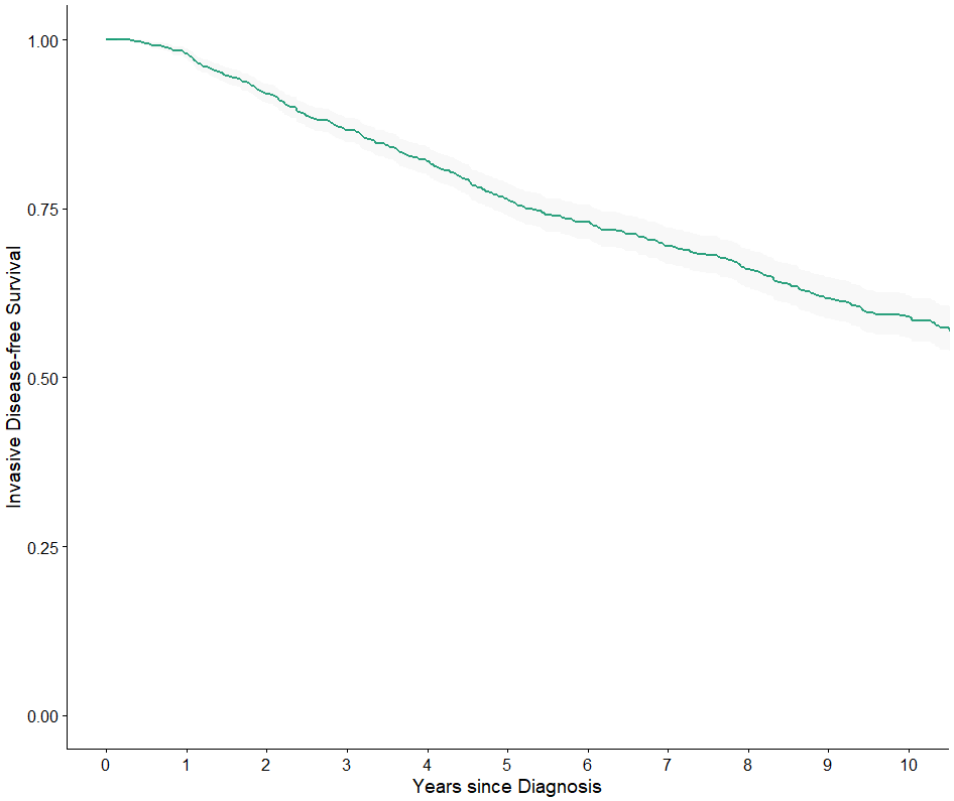


Figure C: 10-year Overall Survival by menopausal status – High Risk MonarchE patients

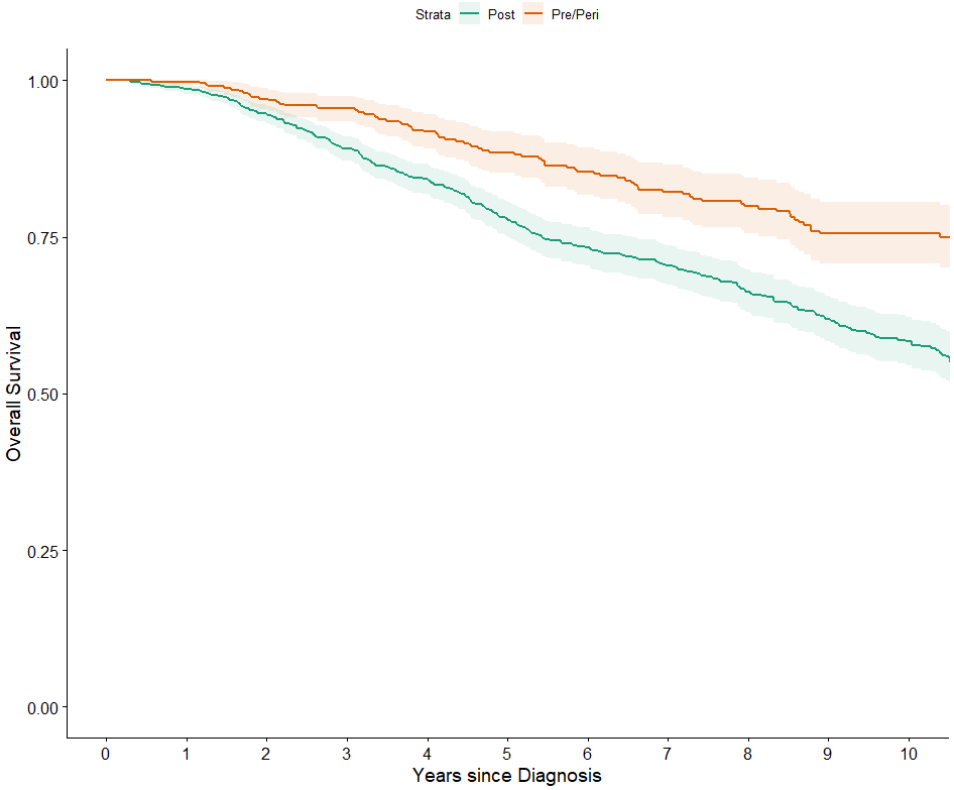


Figure D: 10-year Invasive Disease-free Survival by menopausal status – High Risk MonarchE patients

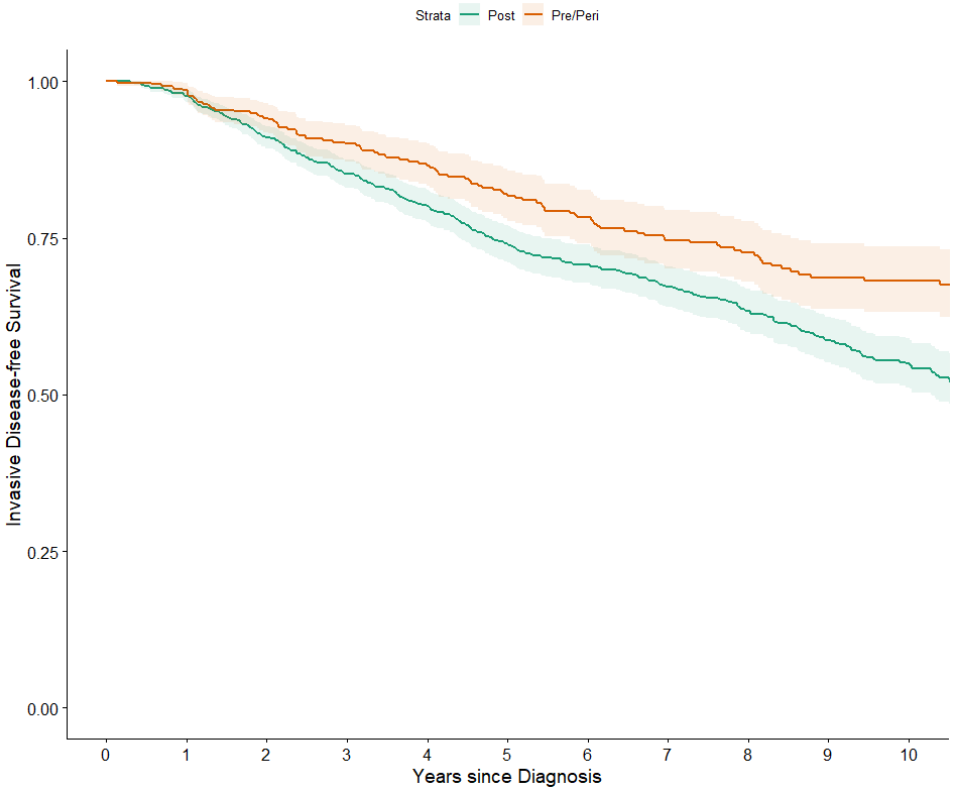


Figure E: 10-year Overall Survival by age group – High Risk MonarchE patients

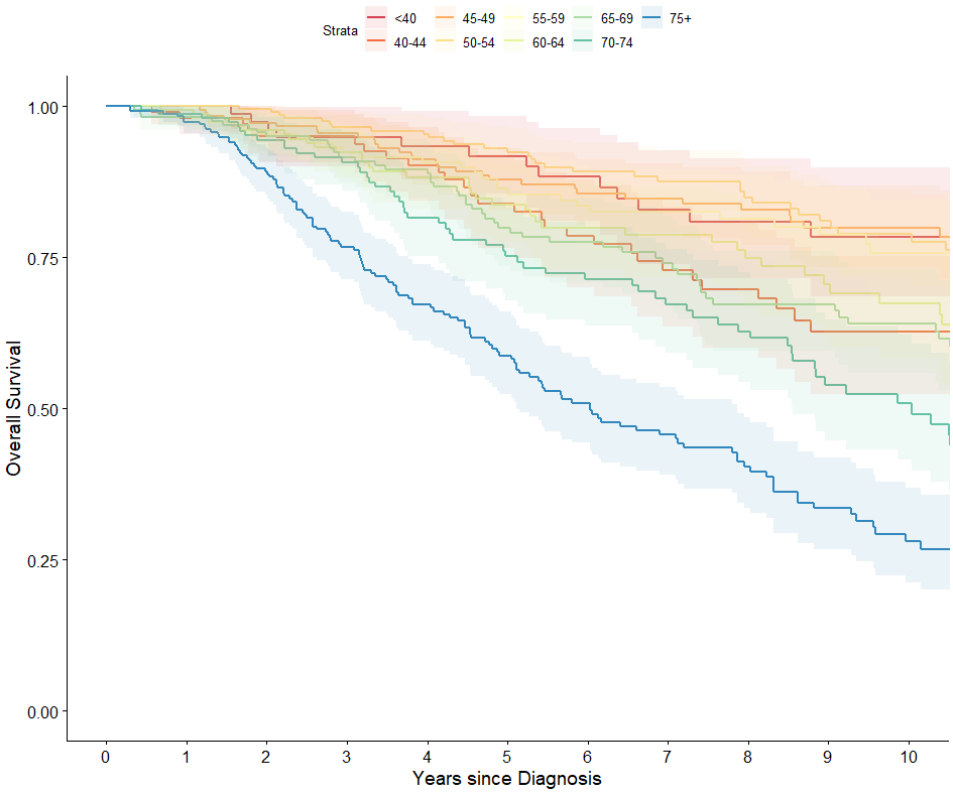


Figure F: 10-year Invasive Disease-free Survival by age group – High Risk MonarchE patients

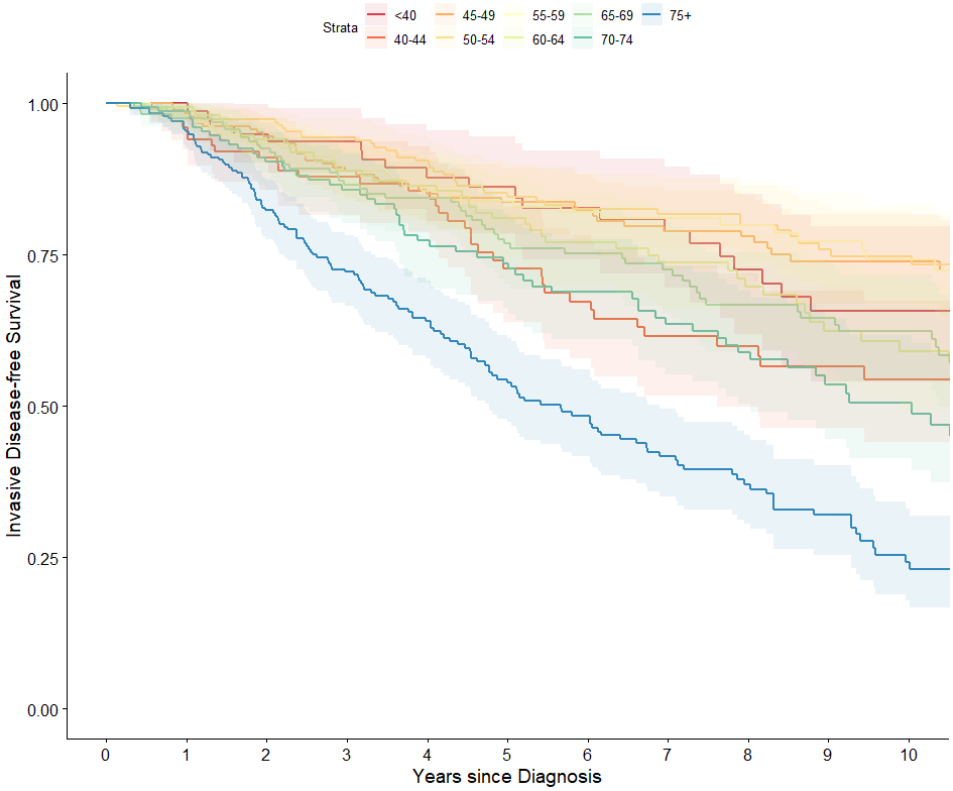


Figure G: 10-year Overall Survival by number of pALNs – High Risk MonarchE patients

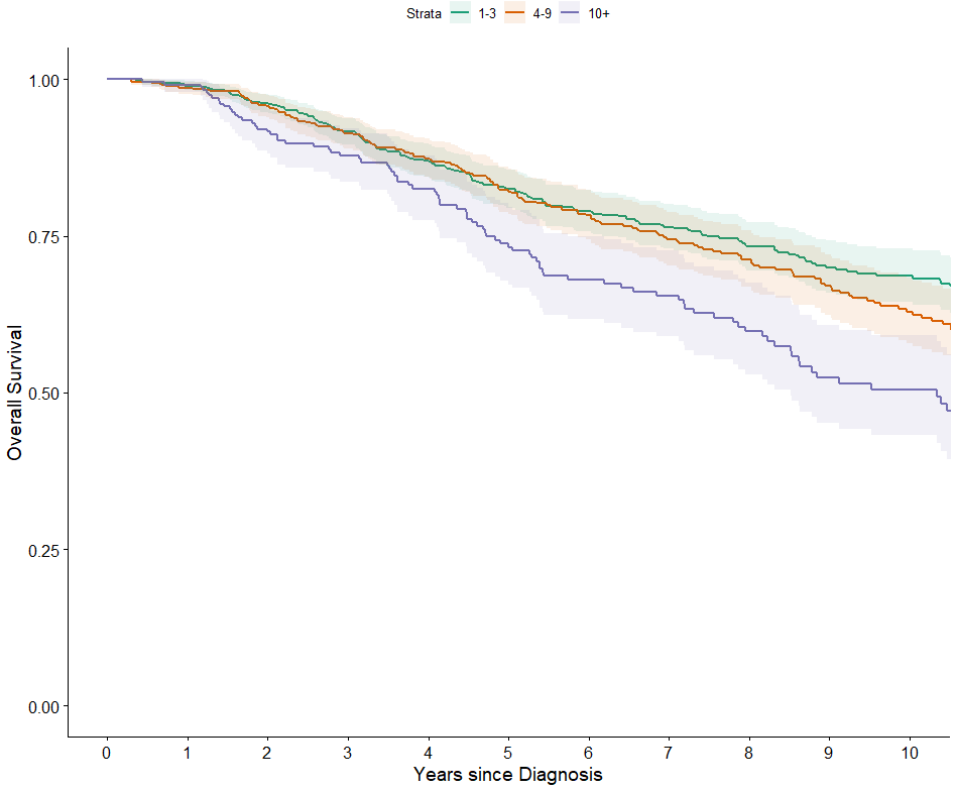


Figure H: 10-year Invasive Disease-free Survival by number of pALNs – High Risk MonarchE patients

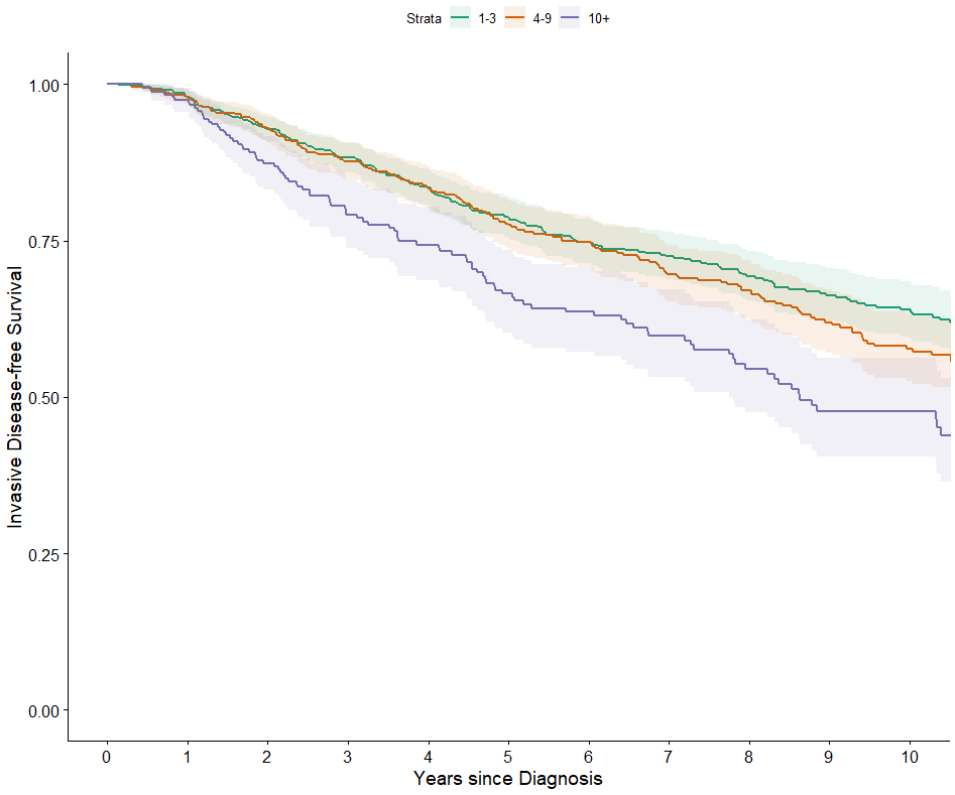


Figure I: 10-year Overall Survival by tumour size – High Risk MonarchE patients

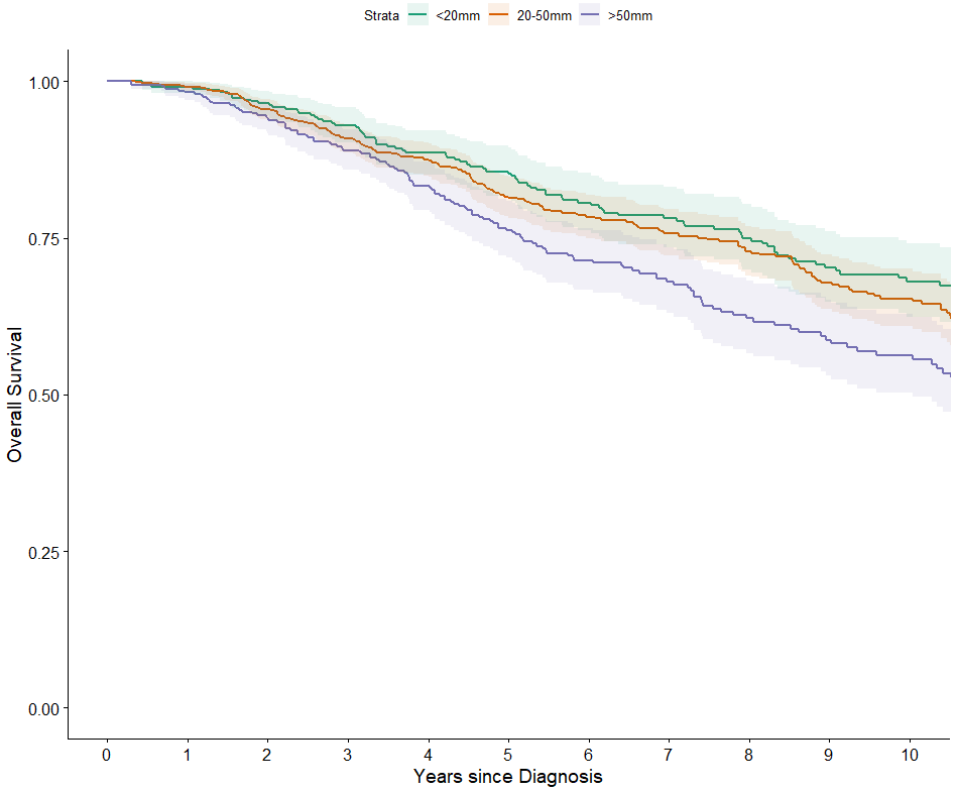


Figure J: 10-year Invasive Disease-free Survival by tumour size – High Risk MonarchE patients

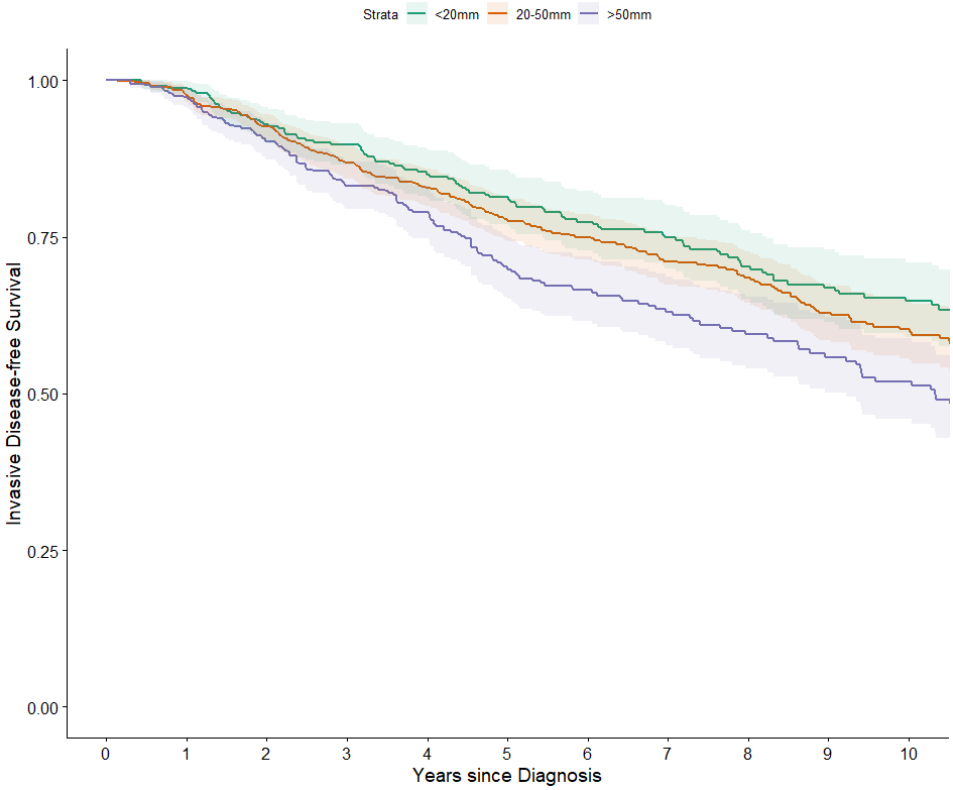


Figure K: 10-year Overall Survival by tumour grade – High Risk MonarchE patients

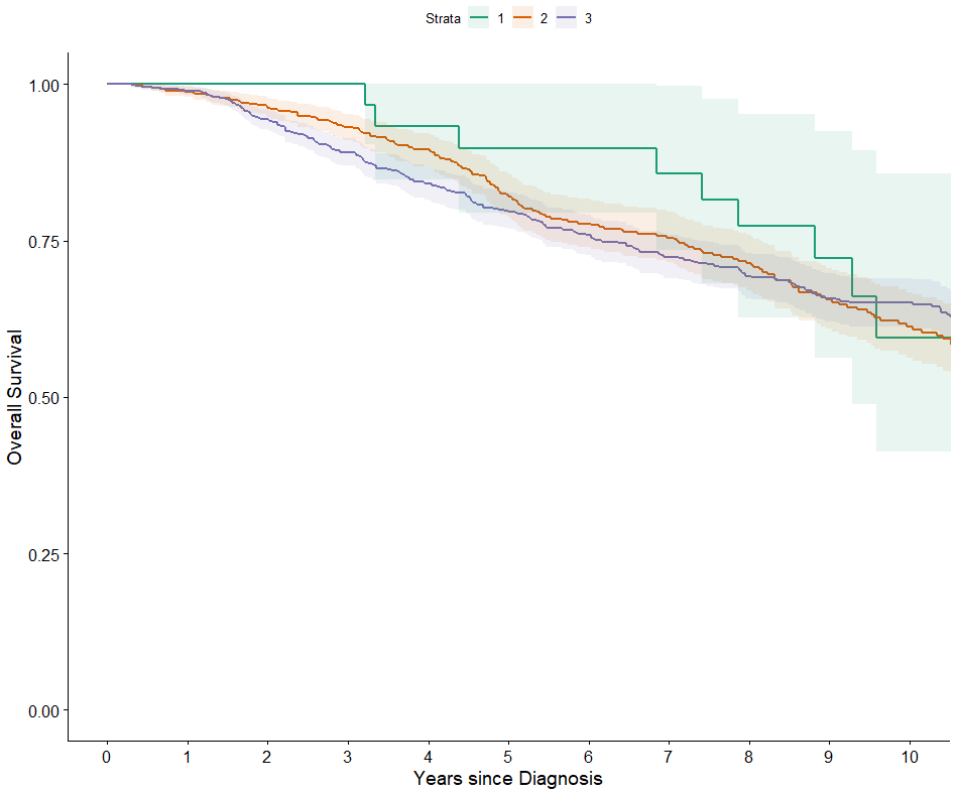
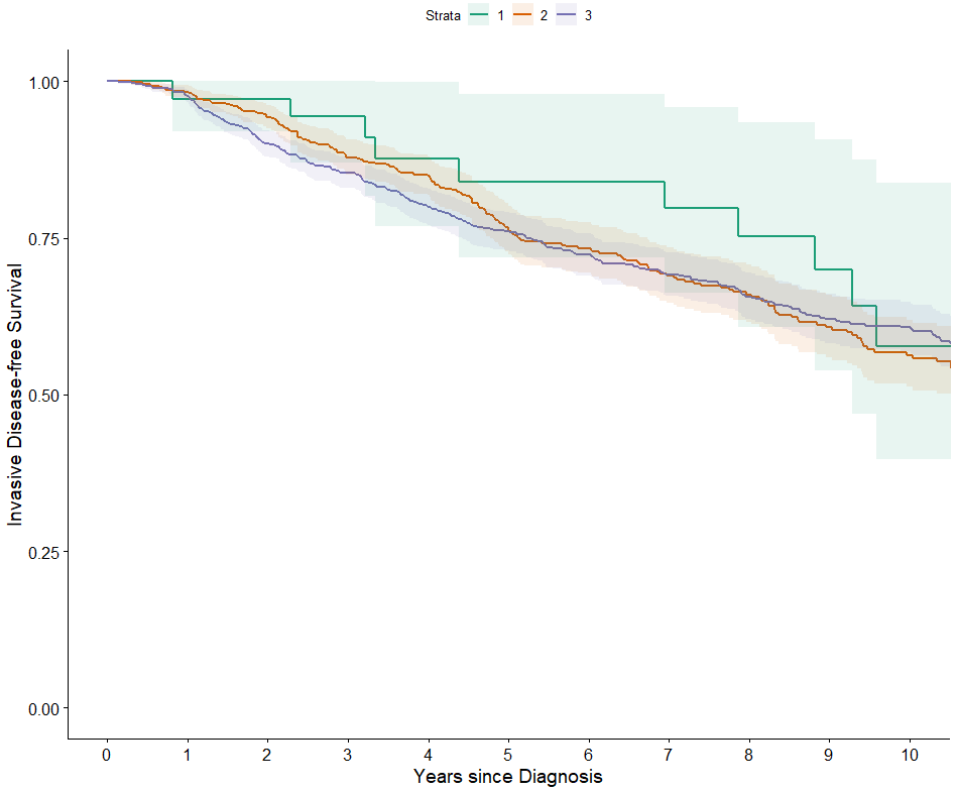


Figure M: 10-year Invasive Disease-free Survival by tumour grade – High Risk MonarchE patients



To make this a Usable Content document, highlight this Revision History page and delete it.

Revision History

Version Number	List of Major Changes
1.0	This is the initial release. This document has been reproduced from the **Observational Study Final Report (non-PASS) Template** v1.0 located in the Leo template library. Title and Revision History pages were added but no content was changed.

Signature Page for VV-CLIN-115152 v1.0

Approval	Lars-Petter Strand Medical Director 25-May-2023 06:29:17 GMT+0000

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