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Bagni, Karin; Chen, Inna M; Johansen, Astrid Z; Dehlendorff, Christian; Jensen, Benny V; Hansen, Carsten P; Preus Hasselby, Jane; Holländer, Niels H; Nissen, Mette; Bjerregaard, Jon K; Pfeiffer, Per; Yilmaz, Mette K; Rasmussen, Louise S; Nielsen, Svend E; Johansen, Julia S

Published in:
European Journal of Cancer Care

DOI (link to publication from Publisher):
10.1111/ecc.13219

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Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Link to publication from Aalborg University

Citation for published version (APA):
Bagni, K., Chen, I. M., Johansen, A. Z., Dehlendorff, C., Jensen, B. V., Hansen, C. P., Preus Hasselby, J., Holländer, N. H., Nissen, M., Bjerregaard, J. K., Pfeiffer, P., Yilmaz, M. K., Rasmussen, L. S., Nielsen, S. E., & Johansen, J. S. (2020). Prognostic impact of Charlson's Age-Comorbidity Index and other risk factors in patients with pancreatic cancer. *European Journal of Cancer Care*, *29*(3), Article e13219. https://doi.org/10.1111/ecc.13219

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Prognostic impact of Charlson's Age-Comorbidity Index and other risk factors in patients with pancreatic cancer

Running title: Risk factors and survival in pancreatic cancer

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Acknowledgments:

The authors would like to acknowledge the patients for their participation in this research. Many thanks to Dan Calatayud, Camilla Palmquist and Pernille Holck Skov for data collection in the

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ECC.13219

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BIOPAC database. Thanks to all the medical and secretariat staff at the Department of Surgical Gastroenterology and Transplantation, Rigshospitalet for their kind assistance.

Conflict of interest for all authors:

None.

Author disclosures:

None.

Funding: This study was supported by grants from The Danish Cancer Society (salary to Karin Bagni).

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Article type : Original Article

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European Journal of Cancer Care (ECC-2019-0001)

Prognostic impact of Charlson's Age-Comorbidity Index and other risk factors in patients with pancreatic cancer

Running title: Risk factors and survival in pancreatic cancer

Abstract

Objectives: Few studies have evaluated the impact of risk factors and comorbidity on overall survival (OS) in patients with pancreatic ductal adenocarcinoma (PDAC). The aim was to investigate the prognostic importance of Charlson's age-comorbidity index (CACI) and other risk factors on prognosis in a clinical real-world cohort of PDAC patients.

Methods: 1159 patients with PDAC who had received at least one cycle of adjuvant or palliative chemotherapy were included from the Danish BIOPAC study. We analyzed OS according to CACI, tobacco smoking, alcohol intake, performance status (PS), BMI, and diabetes. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for OS using Cox proportional hazards regression.

Results: At the end of follow-up 994 (86%) patients had died. The median OS was 298 days for all patients (range 3–3010) and shortest in patients with stage IV. No association with short OS was seen for CACI > 2, diabetes, alcohol abuse, tobacco smoking, hypertension, and high BMI. Multivariate analysis showed that stage (IV vs. I: HR=9.05, 95% CI 5.17-15.84), PS (2 vs. 0: HR=3.67, 2.92-4.61) and treatment with angiotensin-converting-enzyme inhibitors (yes vs. no: HR=1.31, 1.06-1.61) were independent negative prognostic factors.

Conclusions: We found that CACI, diabetes, tobacco smoking, alcohol abuse, hypertension, and high BMI were not associated with OS in a real-world cohort of patients with PDAC treated with chemotherapy. Only stage and PS were prognostic parameters.

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Key Words: BMI, Charlson's Age-Comorbidity Index, diabetes, pancreatic cancer, risk factors, survival

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Introduction

Pancreatic cancer (PC) is one of the most lethal cancers worldwide (Ryan et al. 2014; Hidalgo 2010). It is ranked as the fourth leading cancer related cause of death and the incidence is rising in more developed countries (Siegel et al. 2019; Ferlay et al. 2015). In 2030 PC is expected to be the second leading cause of death of cancer in United States (Rahib et al. 2014). Most patients with PC are diagnosed with advanced stage and the 5-year survival is just 7% (Pancreatic Cancer Treatment NCBI, NIH 2018). The causes of PC are not fully elucidated, but 5-10% of all PC cases have a genetic predisposition (Roberts et al. 2016; Shindo et al. 2017). The strongest evidence of a causative role exists only for tobacco use with a 2-fold increase of PC risk (Bosetti et al. 2012), and cigarette smoking is associated with poor prognosis (Yuan et al. 2017). Type 2 diabetes mellitus (T2DM) is a potential risk factor for PC (Batabyal et al. 2014), but its association with survival is equivocal (Yuan et al. 2015; Jeon et al. 2018). Obesity, chronic pancreatitis, high alcohol intake and blood type A, B or AB are suggested as risk factors for PC (Aune et al. 2012; Larsson et al. 2007; Michaud et al. 2001; Arslan et al. 2010; Duell et al. 2012; Wolpin et al. 2010; Lucenteforte et al. 2012; Wang et al. 2016), but their impact on prognosis is unclear (Kasenda et al. 2014; Yuan et al. 2013; Olson et al. 2010; Zhang et al. 2017; Rizzato et al. 2013; Rahbari et al. 2012).

A group of experts has recommended that age, sex, disease stage, performance status (PS), liver metastases, previous chemotherapy or radiotherapy and previous surgery should be included in future studies of patients with PC to ensure better comparison of outcomes across hospitals/countries (Veer et al. 2018).

PC affects older patients and the median age at diagnosis is 70 years (Howlader et al. 2016). Fit older patients with PC have the same benefits from curative surgery and combination chemotherapy regimens as younger patients (King et al. 2016; Garcia et al. 2017).

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Many patients with PC have comorbidities, e.g. gallbladder diseases, gastric or duodenal ulcers, pernicious anemia, hypertension, and thyroid diseases, however the association with risk of PC is not clear (Olson 2012; Ko et al. 2007). Specific multi-morbidities such as ≥ 2 gastric conditions (heartburn, acid regurgitation, Helicobacter pylori infection, ulcer) and ≥ 3 recently diagnosed metabolic syndrome conditions (obesity, T2DM, hypercholesterolemia, hypertension), as well as combining T2DM with gastric morbidity are associated with the risk of PC (Gomez-Rubio et al. 2017). The prognostic value of these comorbidities is poorly understood, but better PS is associated with longer OS (Vickers et al. 2012; Tas et al. 2013).

Charlson's Age-Comorbidity Index (CACI) measure the relative mortality from various comorbidities (Charlson et al. 1987; Charlson et al. 1994). Precautions exist when using scoring to control for comorbidities including missing weighting for particular comorbidities as well as uncertainty in regard to comprehensiveness of the conditions (Elixhauser et al. 1998). Higher CACI is associated with poorer OS in resected PC patients and patients with unresectable locally advanced PC treated with intra-operative radiotherapy (Asano et al. 2017; Dias-Santos et al. 2015; Cai et al. 2013). There are no studies addressing specifically the prognostic value of CACI and its interplay with other risk factors in a real-world cohort of PC patients undergoing adjuvant or palliative chemotherapy.

Given the morbidity related to chemotherapy and surgery, tools for identifying the fit PC patients for therapy would be of great clinical value. The aim of this study was to investigate the influence of CACI and risk factors on real-world outcomes of PC patients.

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Materials and Methods

The Danish BIOPAC Study "BIOmarkers in patients with Pancreatic Cancer (BIOPAC) – can they provide new information of the disease and improve diagnosis and prognosis of the patients?" (ClinicalTrials.gov ID: NCT03311776; www.herlevhospital.dk/BIOPAC/) was initiated in July 2008 with the aim of conducting translational biomarker research. The BIOPAC study is an open cohort study. All referred patients with diagnosis of PC are eligible for inclusion. The patients included in the BIOPAC study are followed from time of diagnosis and during treatment and follow-up until death. Relevant clinical characteristics of the patients are included in the BIOPAC database. The BIOPAC study protocol is approved by the Danish Ethics Committee (VEK, j.nr. KA-20060113) and the Danish Data Protection Agency (j.nr. 2012-58-0004, HGH-2015-027, I-Suite j.nr. 03960). All patients had received oral and written information before enrolment and gave written consent at baseline according to the guidelines of the Danish Ethics Committee.

BIOPAC is a prospective multi-center biomarker study in which biological samples (blood and cancer tissue) and clinical data are collected prospectively in Danish patients with localised, locally advanced or metastatic PC treated at seven oncological departments and one surgical department in Denmark.

In the present study all patients were >18 years of age and had histologically verified pancreatic ductal adenocarcinoma (PDAC). The patients were either operated (patients with stage I and II) or treated with palliative chemotherapy (patients with stage III and IV) according to national guidelines (www.gicancer.dk). The following baseline characteristics were selected from the BIOPAC database: date of inclusion in the BIOPAC study (1-21 days after PDAC diagnosis), date of death, age, gender, diagnosis, disease stage, PS, body mass index (BMI), use of prescription drugs, smoking status and alcohol intake, Charlson's comorbidity index (CCI), other previous types of cancer, diabetes, hypertension, family history of PC or other cancer, blood type, date of operation and date of first series of adjuvant chemotherapy or 1. line palliative chemotherapy (gemcitabine, nab-paclitaxel + gemcitabine, FOLFIRINOX, capecitabine + gemcitabine, or oxaliplatin + capecitabine). The patients had received at least one cycle chemotherapy.

Definition of covariates

BMI was calculated according to Quetelet´s index (weight/height^2 [kg/m^2]), BMI < 18.5 was classified as underweight, 18.5 to 25 as normal weight and > 25 as overweight; DM included patients with type I or type II treated with anti-diabetics, including oral medication and insulin; CACI was calculated as the CCI after adding 1 point for each time age exceeded 40 years by 10

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years (Charlson et al. 1987; Charlson et al. 1994); tobacco smoking (ever smokers); alcohol abuse (defined as >7 units per week for women and >14 units per week for men); hypertension (i.e. treated with medicine against hypertension); and blood type (blood type 0 vs. other).

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Statistical methods

OS was calculated as the time elapsed between the time of histologic diagnosis and the date of death or the date of last follow-up. Time to death was illustrated with Kaplan-Meier curves. Cox proportional hazard regression was used for univariate and multivariate analyses. Results were summarized by hazard ratios (HRs) and 95% confidence intervals (CIs). In the main analysis only complete cases were used. In a sensitivity analysis the substantive model compatible fully conditional specification multiple imputation approach proposed by Bartlett (Bartlett et al. 2015) was used to address the issue with missing values. P-values less than 5% were considered as statistically significant. All analyses were done in R version 3.4.1.

Results

Demographics of the population

1641 patients were included in the BIOPAC study from July 2008 to July 2017. 1272 patients had PDAC, 75 had ampullary cancer, 41 had intraductal papillary mucinous neoplasm (IPMN), 40 had chronic pancreatitis, 95 had other upper gastrointestinal cancer, 18 had neuroendocrine tumor and 100 had other benign lesions. 123 of the patients with PDAC were excluded from the present study since they did not receive any treatment (n=51), their stage was unknown (n=41) or CACI could not be calculated (n=21). Therefore 1159 patients (median age 67 years, range 37 – 89 years) with PDAC were included in our analysis (Fig. 1). Their demographic data, including risk factors, are shown in Table 1. 406 (35%) patients had stage I or II disease, 187 (16%) had stage III and 566 (49%) had stage IV. 446 (34%) were >69 years old, 424 (36%) had PS 0, 335 (29%) were overweight, 294 (25%) had diabetes, 448 (38%) had CACI <3, 708 (61%) were present or earlier tobacco smokers, 248 (22%) had an alcohol consumption higher than the recommendations, and 409 (35%) had hypertension.

Clinical parameters and overall survival

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At the end of follow-up 994 (86%) patients had died. The median survival was 298 days (95% CI 272-325) for all patients, 676 days (95% CI 592-783) for stage I+II, 309 days (95% CI 262-347) for stage III, and 185 days (95% CI 169-204) for patients with stage IV.

Survival curves (all patients or divided into stages) according to age and PS (Figure 2), BMI and diabetes (Figure 3), CACI and hypertension (Figure 4) demonstrated that age, PS, CACI and hypertension had impact on OS for all patients. Only PS had impact on OS in the different stage groups. CACI had impact on OS for stage III and IV and hypertension for stage I+II and IV.

Survival curves (all patients or divided into stages) according to sex, CCI, tobacco smoking, alcohol abuse, use of ACE-inhibitors, and blood type (Supplement Figures 1-6) showed that only tobacco smoking and treatment with ACE-inhibitors were associated with short OS for stage I-II.
Table 2 shows univariate analysis of association between the clinical characteristics and OS. Higher age (>69 vs. <50 years: HR=1.50, 95% CI 1.07- 2.09), higher stage (Stage IV vs. I: HR=8.31, 5.02-13.75; III vs. I: HR=5.14, 3.06-8.60; and II vs. I: HR=2.12, 1.28-3.51), higher PS (PS 2+ vs. 0: HR=3.11, 2.53-3.81; 1 vs. 0: HR=1.56, 1.36-1.80), tobacco smoking (HR=1.17, 1.01-1.34), CACI score (3-5 vs. 0: HR=1.60, 1.10-2.34; and >5 vs. 0: HR=1.83, 1.17-2.88), CCI (>1 vs. 0: HR=1.29, 1.10-1.52), hypertension (yes vs. no: HR=1.23, 1.08-1.40), and treatment with ACE inhibitors (HR=1.25, 1.04-1.50) were all associated with shorter OS. Diabetes, blood type, and excessive alcohol drinking and high BMI were not significantly associated with shorter OS.

Multivariate analyses including the significant parameters with either CCI or CACI, respectively, are presented in Table 2. Stage (Stage IV vs. I: HR=9.17, 95% CI 5.24-16.07; III vs. I: HR=5.17, 2.92-9.18; and II vs. I: HR=1.99, 1.13-3.49), poorer PS (>2 vs. 0: HR=3.66, 2.91-4.60; 1 vs. 0: HR=1.50, 1.29-1.75) and treatment with ACE inhibitors (HR=1.27, 1.03-1.58) were associated with OS in the multivariate analysis with CACI. Similar results were found if CCI were included in the multivariate analysis. Age, tobacco smoking and CACI/CCI were not significant in the multivariate analysis.

Since some of the variables had missing values (PS 10%, BMI 4%, diabetes 1%, tobacco use 9%, alcohol abuse 8%, hypertension 6% and blood type 19%) we considered multiple imputations by means of "substantive model for multiple imputation of covariates by fully conditional specification" (Bartlett et al. 2015). The results showed no substantial difference from the complete case analysis (Table 3).

Patients´ previous history of cancer and family disposition to cancer

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208 (18%) of the PDAC patients had a previous history of other cancer before PDAC diagnosis. The most common types were breast (20%), colorectal (12%), prostate (11%), uterus (5%) and ovarian cancer (4%). 29% of the PDAC patients had a known family cancer disposition; the most common were PC (13%), colorectal (21%), breast (21%) and lung cancer (17%) (Supplement Figure 7).

Discussion

This population-based study demonstrated that high CACI, diabetes, tobacco smoking, alcohol abuse, hypertension, and high BMI have no independent prognostic impact on mortality in a large real-world cohort of PDAC patients treated with adjuvant or palliative chemotherapy. Our results confirmed that advanced stage and poor PS have significant negative effects on mortality. These data indicate that older PDAC patients or those with significant comorbidity should not automatically be excluded from surgery or chemotherapeutic treatment.

Comorbidities are common in cancer patients and the prevalence increases with age. CACI, which combines age and comorbidity, is the most used index in longitudinal studies for estimating relative risk of death from prognostic clinical covariates (Charlson et al. 1987). The use of comorbidity indices is under discussion for cancer patients with low survival rates such as PDAC. Therefore, new prognostic scales should be developed for such patient groups also taking into account the toxicity of chemotherapy (Kos et al. 2014). CACI was useful in predicting outcome after pancreatectomy in 497 patients with PDAC (Dias-Santos et al. 2015). A CACI score >4 was predictive for increased duration of hospitalization and risk of postoperative complications, and a 3-fold higher risk of death within the first year was found in patients with a CACI score ≥6. In 379 patients who underwent resection for PC the CACI score was an independent prognostic factor for short- and long-term outcome and patients with CACI <4 had better compliance for postoperative adjuvant chemotherapy than patients with CACI ≥4 (Asano et al. 2017). In 194 patients with locally advanced PDAC treated with intraoperative radiotherapy combined with chemotherapy a CACI of ≤3 and treatment with chemotherapy predicted improved OS (Cai et al. 2013).
Our results are in accordance with previous studies demonstrating that pretreatment PS is an independent prognostic factor for survival for patients with PDAC across all stages (Vickers et al. 2012; Tas et al. 2013).

BMI is associated with increased risk of developing PC (Aune et al. 2012; Larsson et al. 2007; Michaud et al. 2001; Arslan et al. 2010). However, few studies with conflicting results have evaluated the impact of BMI on survival of PC patients (Kasenda et al. 2014; Yuan et al. 2013; Olson et al. 2010). Limited information on weight loss and its influence is a possible reason for these contradictory findings. Hypertension is one of the most common comorbidities in cancer

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patients (Piccirillo et al. 2004). Preclinical studies have shown that renin-angiotensin system inhibitors, including ACE inhibition decrease tumor growth and tumor-associated angiogenesis, and inhibit metastasis in various cancer types (Ager et al. 2008). Despite biologically plausible mechanisms, epidemiological studies in this area have shown limited and inconsistent results (Mandilaras et al. 2017; Song et al. 2017). Our results showed a significant independent negative impact of treatment with ACE inhibitors on OS in PDAC patients.

We did not find independent impact on OS for differences in age in our population. Thus, advanced age should not preclude patients from receiving surgery or chemotherapy, and treatment decisions should be based on the physiological rather than the chronological age.

Diabetes was not associated with poor OS in our study. Others have shown that PC patients with long-term diabetes (>4 years) had decreased survival compared with those without diabetes, whereas short-term diabetes was not associated with reduced survival, demonstrating a relationship between persistent glucose intolerance, chronic inflammation and aggressiveness (Yuan et al. 2015). However, results are not consistent (Jeon et al. 2018) and there is a need for more detailed studies addressing the different impact of long-term and recent-onset diabetes, respectively on OS in patients with PC patients.

Our study has limitations which should be recognized. First, our study was retrospective. Second, although most data were generated prospectively in the medical records, review and re-categorization of unstructured data might introduce bias due to the differences in the accuracy or completeness of the recollections retrieved from the patient files. Potential mistakes during data collections and dialing errors into our multicenter database cannot be excluded, although our records were thoroughly quality-checked by two separate authors. Furthermore, we did not have the possibility to distinguish between IDDM and NIDDM, but it is likely that most of the patients had T2DM. Dietary information and past medical conditions, like chronic pancreatitis could affect the mortality of PDAC patients, were not considered here due to incomplete information. Another limitation is that the analysis did not include the type of chemotherapy used and we cannot rule out that our findings may have been influenced in part by differences in chemotherapy. Despite these limitations the current clinical real-world cohort of 1159 patients with PDAC treated in the period 2008 to 2017 with chemotherapy is, to the best of our knowledge, the only nationwide multicenter based population study on consecutive PDAC patients to describe the association of CACI and other risk factors with mortality.

In summary, we showed that CACI, diabetes, tobacco smoking, alcohol abuse, and BMI had no significant prognostic effect on mortality in PDAC patients treated with chemotherapy in routine care setting. We confirmed that advanced cancer stage and poor PS were associated with increased

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mortality in patients with PDAC. These are clinically relevant findings as regards to the management of medical treatment of PDAC patients.

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Table 1. Clinical characteristics of the 1159 patients with PDAC.

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; CACI, Charlson's Age-Comorbidity Index; CCI, Charlson's Comorbidity Index.

PDAC patients			**Stage**		
Covariates		All	I – II	III	IV
N		1159	406 (35)	187 (16)	566 (49)
Sex (%)	**Female**	531 (46)	193 (48)	88 (47)	250 (44)
	Male	628 (54)	213 (52)	99 (53)	316 (56)
Age (%)	**<50**	47 (4)	19 (5)	8 (4)	20 (3)
	50 – 69	666 (58)	248 (61)	103 (55)	315 (56)
	>69	446 (38)	139 (34)	76 (41)	231 (41)
Median (range)		67 (37 – 89)	69 (40 – 88)	67 (38 – 88)	66 (37 – 89)
PS (%)	**0**	424 (36)	164 (41)	61 (32)	199 (35)
	1	486 (42)	122 (30)	93 (50)	271 (48)
	>1	137 (12)	30 (7)	24 (13)	83 (15)
	Unknown	112 (10)	90 (22)	9 (5)	13 (2)

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BMI (%)	**<18.5**	63 (6)	21 (5)	10 (5)	32 (5)
	18.5 – 25	708 (61)	252 (62)	124 (67)	332 (59)
	>25	335 (29)	112 (28)	45 (24)	179 (32)
	Unknown	53 (4)	22 (5)	8 (4)	23 (4)
Diabetes (%)	**No**	854 (74)	291 (71)	135 (72)	428 (76)
	Yes	294 (25)	113 (28)	51 (27)	130 (23)
	Unknown	11 (1)	2 (1)	1 (1)	8 (1)
CACI (%)	**0**	36 (3)	17 (4)	7 (4)	12 (3)
	1-2	412 (35)	152 (38)	55 (30)	205 (36)
	3 – 5	643 (56)	215 (53)	113 (60)	315 (55)
	>6	66 (6)	22 (5)	12 (6)	32 (5)
	Unknown	2 (0)	0 (0)	0 (0)	2 (1)
CCI (%)	**0**	602 (52)	215 (53)	98 (53)	289 (51)
	1	325 (28)	119 (30)	51 (27)	155 (27)
	>1	232 (20)	72 (17)	38 (20)	122 (22)
Tobacco (%)	**No**	347 (30)	139 (34)	51 (27)	157 (28)
	Yes	708 (61)	239 (59)	117 (63)	352 (62)
	Unknown	104 (9)	28 (7)	19 (10)	57 (10)
Alcohol abuse (%)	**No**	806 (70)	295 (73)	131 (70)	380 (67)
	Yes	248 (22)	82 (20)	38 (20)	128 (23)
	Unknown	105 (8)	29 (7)	18 (10)	58 (10)
Hypertension (%)	**No**	683 (59)	238 (58)	122 (65)	323 (57)
	Yes	409 (35)	148 (37)	52 (28)	209 (37)
	Unknown	67 (6)	20 (5)	13 (7)	34 (6)
Blood Type (%)	**Type 0**	317 (27)	120 (30)	59 (31)	138 (24)
	Other	625 (54)	239 (59)	88 (47)	298 (53)
	Unknown	217 (19)	47 (11)	40 (22)	130 (23)

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Table 2. Univariate and multivariate analysis for OS according to risk factors.

Univariate analysis					Multivariate analysis with CCI			with CACI		
Covariates		**HR**	**95%CI**	**p–value**	**HR**	**95%CI**	**p–value**	**HR**	**95%CI**	**p–value**
Sex	**Female**	Ref								
	Male	1.04	[0.92 – 1.18]	0.53						
Age	**<50**	Ref			Ref			Ref		
	50 – 69	1.24	[0.89 – 1.72]	0.21	1.21	[0.84 – 1.76]	0.30	1.12	[0.56 – 2.22]	0.75
	>69	1.50	[1.07 – 2.09]	0.02	1.22	[0.83 – 1.78]	0.31	1.05	[0.52 – 2.14]	0.89
Stage	**I**	Ref			Ref			Ref		
	II	2.12	[1.28 – 3.51]	0.004	1.99	[1.13 – 3.49]	0.02	1.98	[1.13 – 3.49]	0.02
	III	5.13	[3.06 – 8.60]	<0.001	5.17	[2.92 – 9.18]	<0.001	5.21	[2.93 – 9.24]	<0.001
	IV	8.31	[5.02 –13.75]	<0.001	9.05	[5.17–15.84]	<0.001	9.17	[5.24–16.07]	<0.001
PS	**0**	Ref			Ref			Ref		
	1	1.56	[1.36 – 1.80]	<0.001	1.50	[1.29 – 1.75]	<0.001	1.49	[1.28 – 1.74]	<0.001
	>1	3.11	[2.53 – 3.81]	<0.001	3.67	[2.92 – 4.61]	<0.001	3.66	[2.91 – 4.60]	<0.001
BMI	**<18.5**	Ref								
	18.5 – 25	0.82	[0.62 – 1.09]	0.17						
	>25	0.84	[0.63 – 1.12]	0.23						
Diabetes	**No**	Ref								
	Yes	1.00	[0.86 – 1.15]	0.98						
CACI	**0**	Ref						Ref		
	1-2	1.34	[0.91 – 1.98]	0.13				1.05	[0.47 – 2.35]	0.90
	3-5	1.60	[1.10 – 2.34]	0.02				1.15	[0.50 – 2.64]	0.75
	>6	1.83	[1.17 – 2.88]	0.009				1.37	[0.56 – 3.39]	0.49
CCI	**0**	Ref			Ref					
	1	1.06	[0.92 – 1.23]	0.41	0.96	[0.82 – 1.14]	0.67			
	>1	1.29	[1.10 – 1.52]	0.002	1.07	[0.89 – 1.30]	0.47			
Tobacco	**No**	Ref			Ref			Ref		
	Yes	1.17	[1.01 – 1.34]	0.03	1.10	[0.95 – 1.27]	0.22	1.08	[0.93 – 1.26]	0.29
Alcohol	**No**	Ref								
Abuse	**Yes**	1.03	[0.88 – 1.20]	0.72						
Hyper-	**No**	Ref								
Tension	**Yes**	1.23	[1.08 – 1.40]	0.002						

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ACE Inhibitor	**No**	Ref								
	Yes	1.25	[1.04 – 1.50]	0.016						
Hyper-Tension	**No**	Ref			Ref			Ref		
	Yes	1.31	[1.09 – 1.58]	0.005	1.31	[1.06 – 1.61]	0.01	1.27	[1.03 – 1.58]	0.03
	+ ACEI									
	Yes – ACEI	1.19	[1.02 – 1.38]	0.03	1.13	[0.95 – 1.34]	0.17	1.11	[0.94 – 1.32]	0.22
Blood Type	**Type 0**	Ref								
	Other	1.05	[0.91 – 1.22]	0.50						

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; CACI, Charlson's Age-Comorbidity Index; CCI, Charlson's Comorbidity Index; ACEI, Angiotensin-converting-enzyme inhibitors.

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Table 3. Multiple imputation analysis.

Covariates		HR	95% CI	p – value
Age	<50	Ref		
	50-69	1.21	[0.87 – 1.69]	0.26
	>69	1.22	[0.87 – 1.72]	0.25
Stage	I	Ref		
	II	2.11	[1.26 – 3.51]	0.00
	III	5.09	[3.02 – 8.56]	0.00
	IV	8.50	[5.11 – 14.11]	0.00
PS	0	Ref		
	1	1.49	[1.28 – 1.73]	0.00
	>1	3.25	[2.62 – 4.02]	0.00
Tobacco	No	Ref		
	Yes	1.11	[0.96 – 1.28]	0.16
CCI	0	Ref		
	1	0.96	[0.83 – 1.12]	1.36
	>1	1.11	[0.93 – 1.32]	0.26
Hypertension ± ACEI	No	Ref		
	Yes + ACEI	1.27	[1.04 – 1.55]	0.02
	Yes – ACEI	1.13	[0.95 – 1.34]	0.18

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; CCI, Charlson's Comorbidity Index; ACEI, Angiotensin-converting-enzyme-inhibitor.

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Figure Legends

Figure 1. Flow diagram showing inclusion and exclusion criteria to produce the final study group.
Figure 2. Kaplan-Meier curves showing OS according to age and PS and divided into stage groups
Figure 3. Kaplan-Meier curves showing OS according to baseline BMI and diabetes status divided into stage groups.

Figure 4. Kaplan-Meier curves showing OS according to CACI and hypertension status and divided into stage groups.

Supplement Figure 1. Kaplan-Meier curves showing OS according to gender and divided into stage groups.

Supplement Figure 2. Kaplan-Meier curves showing OS according to CCI scoring and divided into stage groups.

Supplement Figure 3. Kaplan-Meier curves showing OS according to baseline tobacco smoking status and divided into stage groups.

Supplement Figure 4. Kaplan-Meier curves showing OS according to baseline alcohol status and divided into stage groups.

Supplement Figure 5. Kaplan-Meier curves showing OS according to treatment with ACE inhibitors and divided into stage groups.

Supplement Figure 6. Kaplan- Meier curves showing OS according to blood type and divided into stage

groups

Supplement Figure 7. Flowchart showing previous history of cancer (7a) and family disposition to cancer (7b)

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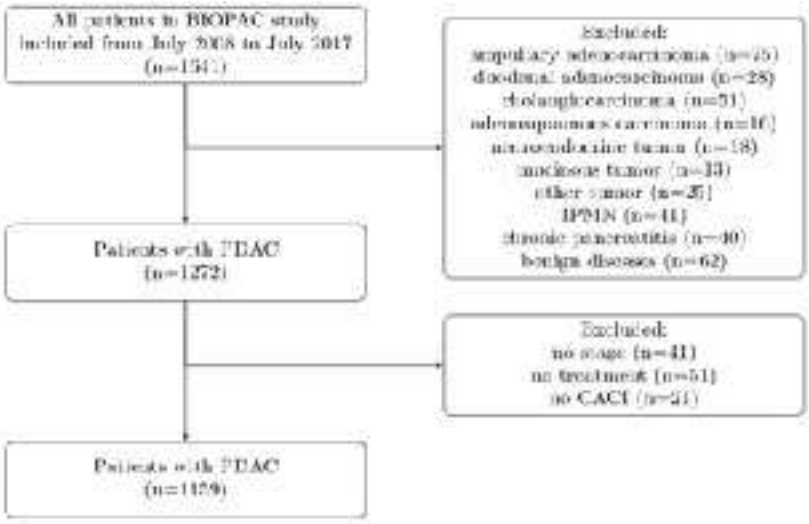

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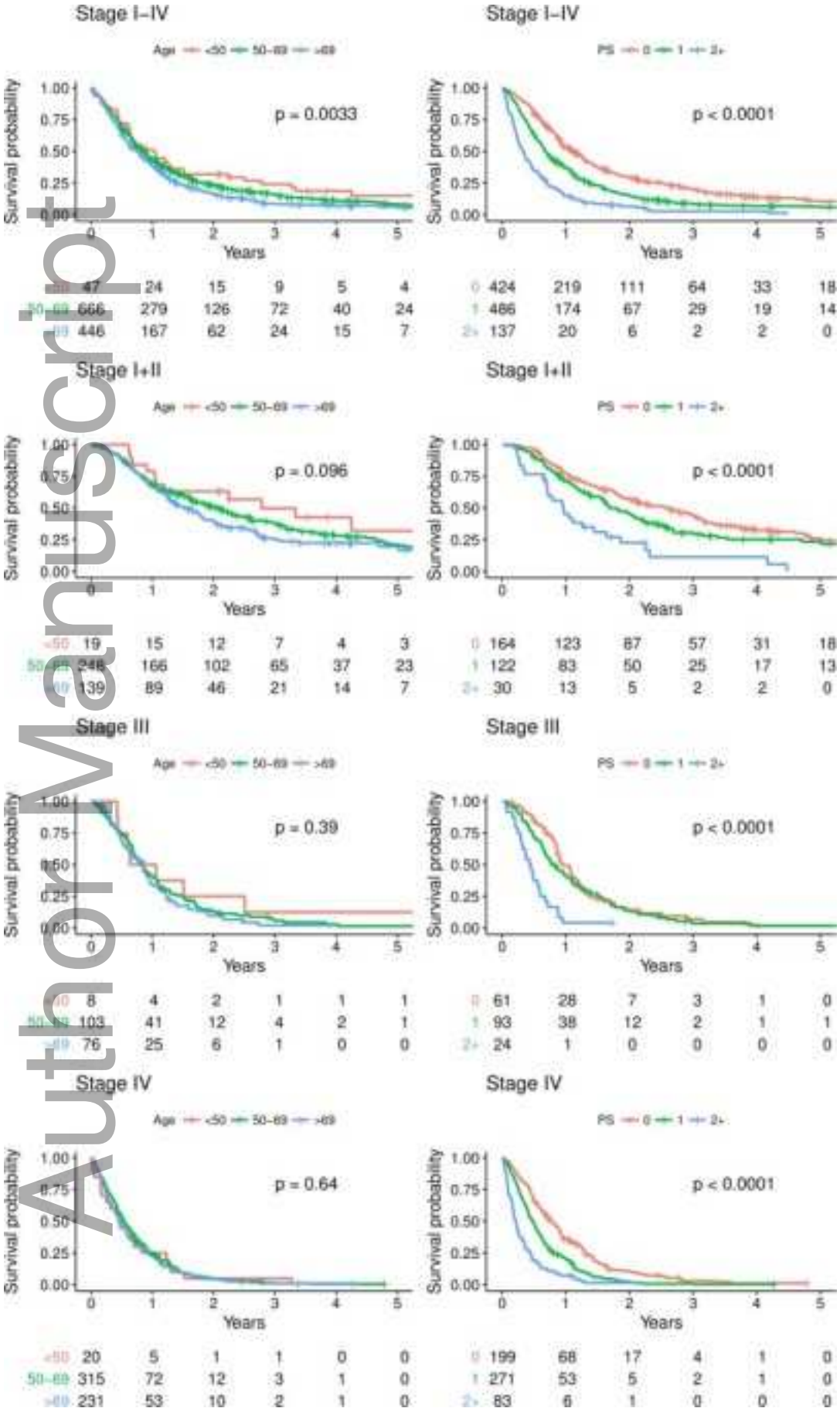

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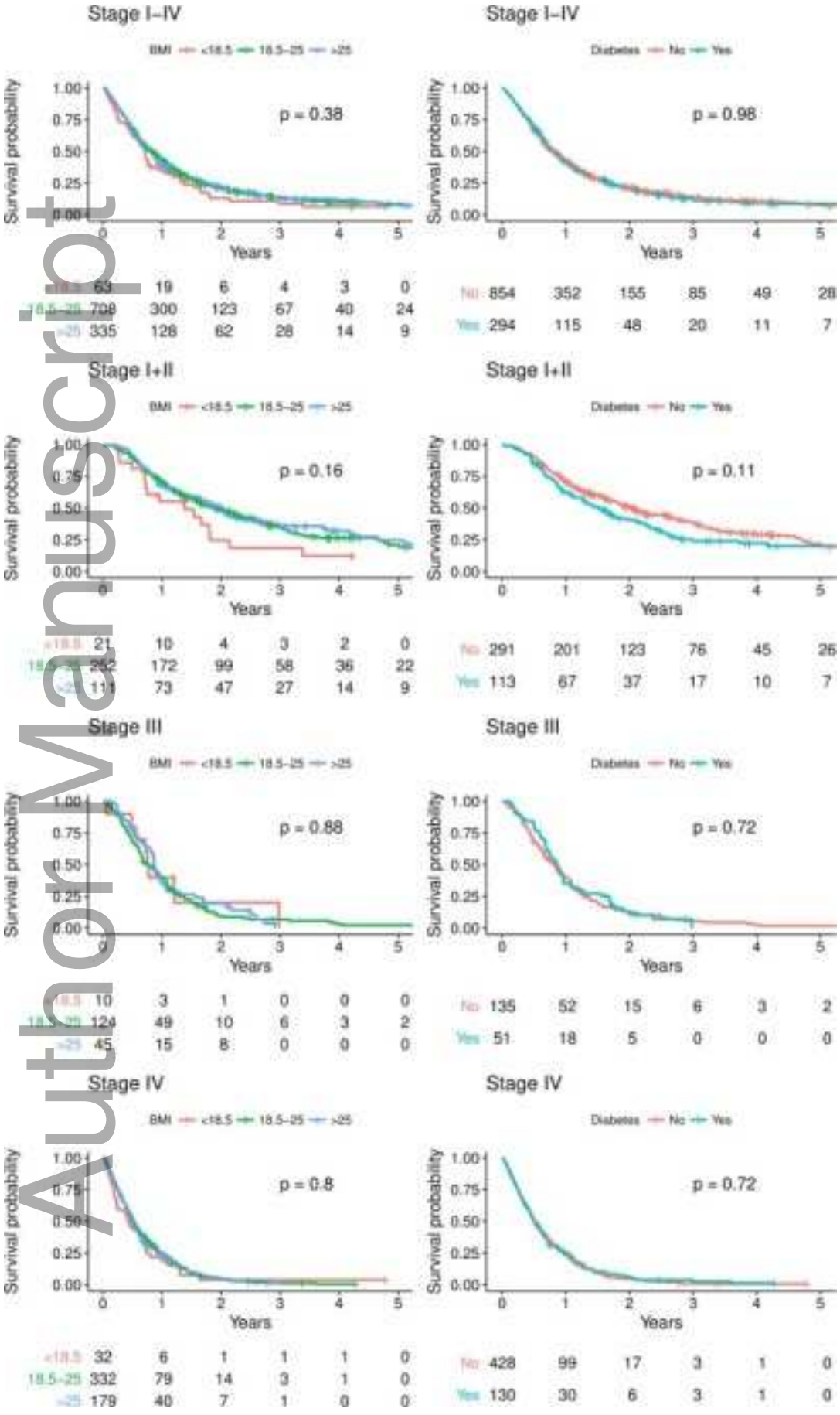

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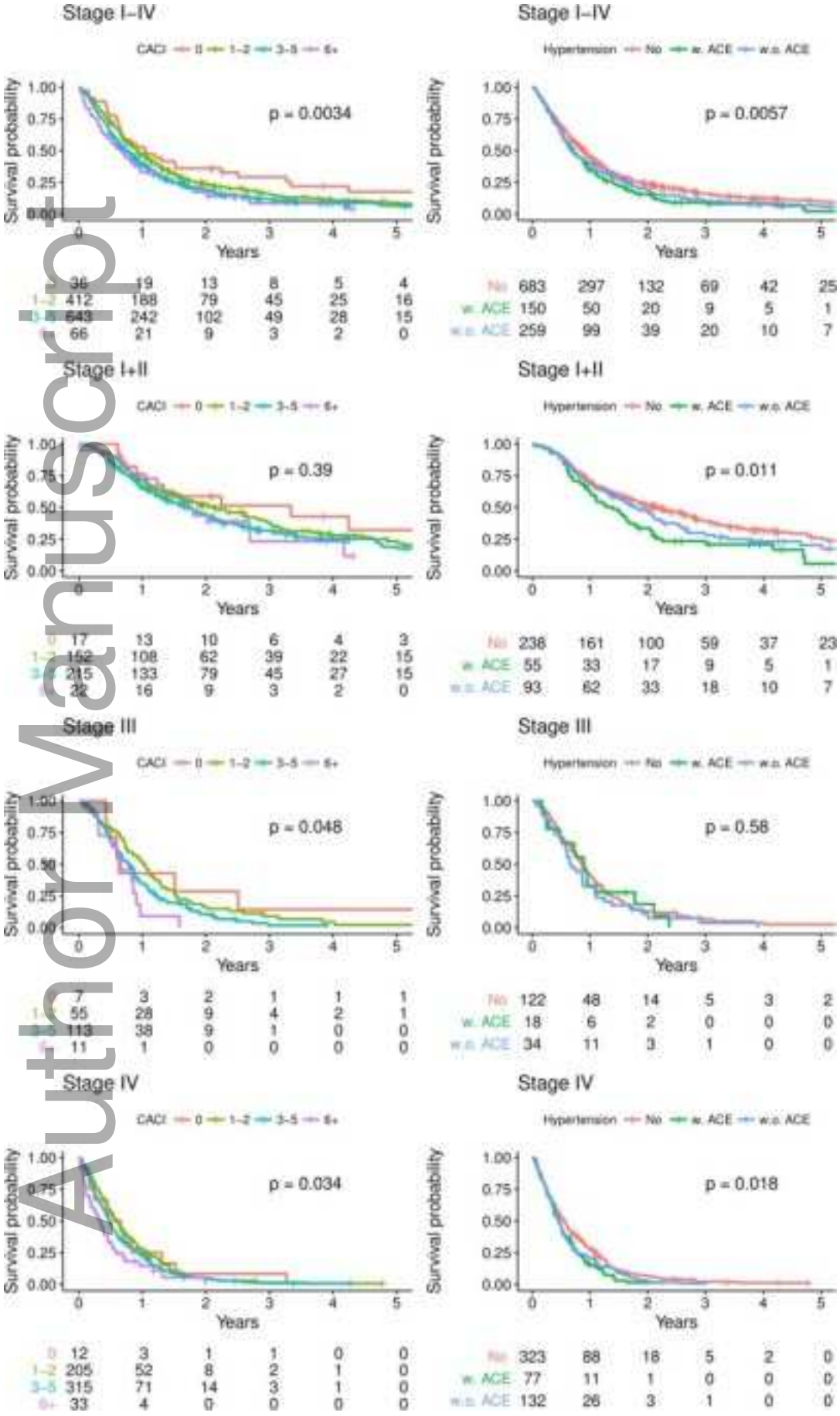

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