Risk Factors For Long-Term Survival in Patients With ypN+M0 Rectal Cancer After Radical Anterior Resection

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Research Article

Keywords: angiotensin-converting enzyme inhibitors, lymph node metastasis, lymph node yield, negative lymph node count, rectal cancer, renin-angiotensin system

Posted Date: August 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-688551/v1

Version of Record: A version of this preprint was published at BMC Gastroenterology on March 26th, 2022. See the published version at https://doi.org/10.1186/s12876-022-02226-9.

Abstract

Background: Regional lymph node metastases are the main adverse prognostic factor in patients with rectal cancer without distant metastases. There are discrepancies, however, regarding additional risk factors in the group of ypN+M0 patients.

The purpose of the study was to assess clinical and pathological factors affecting long-term oncological outcomes in the group of ypN+M0 patients after radical rectal anterior resection.

Methods: 112 patients with ypN+M0 rectal cancer after neoadjuvant therapy and radical anterior resection were subject to a retrospective analysis. The effect of potential factors on survival was assessed with the use of Kaplan-Meier curves together with a log-rank test and multiple factor Cox proportional hazards model.

Results: In the multiple factor Cox analysis, adverse factors affecting OS were: the use of angiotensin-converting enzyme inhibitors (ACEIs) (HR: 3.059, 95% CI: 1.349-6.934, p= 0.007) and past <=3 cycles of adjuvant chemotherapy (HR: 2.833, 95% CI: 1.289-6.229, p= 0.01). For DFS, significant adverse factors were: the use of ACEIs (HR: 3.11, 95%CI: 1.01-9.56, p= 0.047), presence of perineural invasion (HR: 7.27, 95% CI: 2.74-19.3, p< 0.001) and occurrence of postoperative complications (HR: 6.79, 95% CI: 2.09-22.11, p= 0.001), while a positive factor was the negative lymph node (NLN) count >7 (HR: 0.33, 95% CI: 0.12-0.88, p= 0.026).

Conclusions: The use of ACEIs may have a negative effect on long-term treatment outcomes in patients with ypN+M0 rectal cancer. In this group of patients, the NLN count seems to be an important prognostic factor, as well.

Background

Regional lymph node metastases are the main adverse prognostic factor in patients with colorectal cancer without distant metastases. [1] However, reports on the risk factor of long-term survival in the group ypN + are not consistent. It turns out that the assessment of nodal staging according to the TNM classification does not clearly stratify subjects after neoadjuvant therapy with regard to long-term survival. [2] Therefore, attempts have been made to assess other factors, such as lymph node ratio (LNR), log odds of positive nodes (LODDS), positive lymph nodes (PLN), or negative lymph nodes (NLN). Their prognostic value, however, has not been finally established. [1, 3] A separate issue is the minimum lymph node yield (LNY), owing to which underestimation of nodal staging may be avoided. Some authors deny the adverse effect of low LNY on survival, and even suggest that it is related to a good response to neoadjuvant therapy. [4] So far, the effect of comorbidities and the medication used therein, such as metformin or renin-angiotensin system inhibitors (RASI), on the treatment outcomes has not been clarified. [5, 6] There are few publications on this issue. It has also been shown that postoperative complications, especially anastomotic leakage (AL) after rectal anterior resection (AR) may have a significant effect on survival. [7]

The purpose of the study was a retrospective assessment of clinical and pathological factors affecting long-term oncological outcomes in patients with rectal cancer at ypN + M0, after neoadjuvant therapy and radical (R0) AR.

Methods

Patients

A retrospective analysis was performed on 112 patients with ypN + M0 rectal cancer post neoadjuvant therapy and radical (R0) AR, treated at the National Research Institute of Oncology in Gliwice in 2008–2016. The process of the study group formation in presented on the chart in Fig. 1.

Patient characteristics is presented in Table 1. Comorbidities were assessed separately, as well as on the basis of the Charlson comorbidity index (CCI). [8] Distant metastases were considered synchronous if occurred up to 3 months after surgery.

Table 1
Patient characteristics

Variable		n (%) mean (SD)*
Sex	Females	42 (37.5)
	Males	70 (62.5)
Age (years)		62,21 (10.32)*
BMI (kg/m^2)		26,64 (5.05)*
CAD		5 (4.5)
AH		45 (40.2)
DIAB		18 (16.1)
CCI > 2		25 (22.3)
Alpha-blockers		3 (2.7)
Beta-blockers		26 (23.2)
ACEIs		19 (17)
Calcium channel blockers		14 (12.5)
Diuretics		10 (8.9)
ARBs		9 (8)
Metformin		7 (6.2)
Glimepiride		7 (6.2)
Gliclazide		5 (4.5)
cT	1	1 (0.9)
	2	10 (8.9)
	3	99 (88.4)
	4	2 (1.8)

*continuous variable, BMI- body mass index, CAD- coronary artery disease, AH- arterial hypertension, DIAB- diabetes mellitus, CCI- Charlson comorbidity index, ACEIs- angiotensin-converting enzyme inhibitors, ARBs- angiotensin receptor blockers, CRT- chemoradiotherapy, RT- radiotherapy, Time RT-S- time from radiotherapy completion to surgery, AL- anastomotic leakage, G- histological tumour grade, TRG- tumour regression grade, PLN- positive lymph nodes, NLN- negative lymph nodes, LNY- lymph node yield, LNR- lymph node ratio, LODDS- log odds of positive lymph nodes, ENE- extranodal extension, LVI- lymphovascular invasion, PNI- perineural invasion, CT- chemotherapy, SD- standard deviation

Variable		n (%) mean (SD)*
cN+		91 (81.2)
Distance from the anal verge (cm)	0–5	42 (37.5)
	6–10	52 (46.4)
	11–15	18 (16.1)
Neoadjuvant	CRT	27 (24.1)
	RT	85 (75.9)
Time RT-S > 6 weeks		45 (40.2)
Loop ileostomy		23 (20.5)
Complications (Clavien-Dindo)	0	73 (65.2)
	1–2	14 (12.5)
	> 2	25 (22.3)
AL	Early AL	16 (14.3)
	Late AL	7 (6.2)
	No leakage	89 (79.5)
ypG	1	5 (4.5)
	2	82 (73.2)
	3	8 (7.1)
	x	17 (15.2)
ypT	0	1 (0.9)
	2	20 (17.9)
	3	91 (81.2)
TRG	0–1	27 (24.1)

*continuous variable, BMI- body mass index, CAD- coronary artery disease, AH- arterial hypertension, DIAB- diabetes mellitus, CCI- Charlson comorbidity index, ACEIs- angiotensin-converting enzyme inhibitors, ARBs- angiotensin receptor blockers, CRT- chemoradiotherapy, RT- radiotherapy, Time RT-S- time from radiotherapy completion to surgery, AL- anastomotic leakage, G- histological tumour grade, TRG- tumour regression grade, PLN- positive lymph nodes, NLN- negative lymph nodes, LNY- lymph node yield, LNR- lymph node ratio, LODDS- log odds of positive lymph nodes, ENE- extranodal extension, LVI- lymphovascular invasion, PNI- perineural invasion, CT- chemotherapy, SD- standard deviation

Variable		n (%) mean (SD)*
	2–3	85 (75.9)
Mucinous component		6 (5.4)
Tumour deposits		29 (25.9)
PLN count		3,59 (3.75)*
NLN count		10,69 (6.16)*
LNY		13,99 (6.79)*
ypN	1	79 (70.5)
	2	33 (29.5)
LNR		0,26 (0.21)*
LODDS		-1,3 (1.18)*
ENE		14 (12.5)
LVI		10 (8.9)
PNI		13 (11.6)
Distal margin (cm)		2,11 (1.61)*
Adjuvant CT		89 (79.5)
Adjuvant CT > 3 cycles		78 (69.6)

*continuous variable, BMI- body mass index, CAD- coronary artery disease, AH- arterial hypertension, DIAB- diabetes mellitus, CCI- Charlson comorbidity index, ACEIs- angiotensin-converting enzyme inhibitors, ARBs- angiotensin receptor blockers, CRT- chemoradiotherapy, RT- radiotherapy, Time RT-S- time from radiotherapy completion to surgery, AL- anastomotic leakage, G- histological tumour grade, TRG- tumour regression grade, PLN- positive lymph nodes, NLN- negative lymph nodes, LNY- lymph node yield, LNR- lymph node ratio, LODDS- log odds of positive lymph nodes, ENE- extranodal extension, LVI- lymphovascular invasion, PNI- perineural invasion, CT- chemotherapy, SD- standard deviation

Procedures

All the patients received neoadjuvant therapy: radiotherapy (RT) at a total dose of 25–42 Gy or chemotherapy (CRT) at a dose of 42–54 Gy combined with one or two cycles of chemotherapy based on 5-fluorouracil. Before surgery, mechanical bowel preparation was performed with the administration of an oral antibiotic and perioperative intravenous antibiotic prophylaxis. AR was performed using laparotomy with total mesorectal excision. End-to-end anastomosis of bowel was performed with a circular stapler. AL, in accordance with the International Study Group of Rectal Cancer, was defined as a deficit at the

anastomotic site leading to a communication between the intra- and extraluminal compartments and/or presence of pelvic abscess near the anastomosis. [9] AL was qualified as early if diagnosed within 30 days of surgery, and as late if occurred after that time. Adjuvant treatment was based on 5-fluorouracil. The histopathological examination was based on standard methods of searching for lymph nodes in the surgical specimen. Tumour regression grade (TRG) was based on the assessment of the degree of fibrosis compared to the residual tumor tissue and ranged from 0 to 3, i.e. 0 (complete response), 1 (< 10% residual tumor), 2 (10–50%) and 3 (> 50%).

Variables

Staging was assessed on the basis of the American Joint Committee on Cancer, TNM Staging System, 8th edition, 2017. LNR was calculated as the PLN to LNY ratio, while LODDS was calculated with the formula ln[(PLN count)/(NLN count)]. In the LODDS and LNR analysis in ypN1c patients, the PLN count was treated as no data and was excluded from this part of the analysis. Additional potential risk factors subject to analysis included: age, sex, body mass index (BMI), presence of comorbidities, CCI, medications used, type of neoadjuvant therapy (RT vs. CRT), time from RT completion to surgery, clinical staging of the disease before treatment, tumour distance from the anal verge, presence of loop ileostomy, occurrence of postoperative complications, TRG, perineural invasion (PNI), lymphovascular invasion (LVI), extranodal extension (ENE), width of distal margin, adjuvant chemotherapy.

Statistical methods

The effect of potential factors on survival was assessed with the use of Kaplan-Meier curves together with a log-rank test and Cox proportional hazards model. The estimation of cut-off points for the parameters related to nodal staging was based on the analysis of Kaplan-Meier curve difference significance for iteratively increased cut-off thresholds. All calculations were made using the statistical package R version 3.5.3.

Results

In the study group, 3- and 5-year overall survival (OS) was 80.4% and 67%, disease-free survival (DFS) was 71.9% and 59.7%, and disease-specific survival (DSS) was 85.5% and 74.4%, respectively. The mean follow-up period in the study group was 57 months. 30-day mortality after surgery was 1.7%. Loop ileostomy during the primary procedure was created in 23/112 (20.5%) of patients. Postoperative complications were observed in 39/112 (34.8%) of patients. AL was observed in 23/112 (20.5%) of patients, including 16/23 (69.6%) early and 7/23 (30.4%) late ALs. In 15/23 (65.2%) cases of AL, anastomosis was separated by performing the Hartmann's procedure. Aside to the above, abnormal wound healing was observed in 6 patients, and there were 3 cases of urinary tract infection, 3 cases of pneumonia, 3 cases of bleeding and 1 case of mechanical obstruction. 19 (17%) patients used angiotensin-converting enzyme inhibitors (ACEIs) at the time of treatment initiation, with 5 patients using ramipril, 5 perindopril, 3 enalapril, 2 lisinopril, 2 trandolapril, 1 cilazapril and 1 imidapril. 9 (8%) patients used angiotensin receptor blockers (ARBs).

Analysis of nodal staging parameters

For the LNY variable, no cut-off point for which Kaplan-Meier curves would significantly differ was found. Similarly, no differences in survival were found while comparing nodal staging (ypN1 vs. ypN2) according to the TNM classification. For the PLN count, significant differences in survival were found only at the cut-off point 11 (< = 11 vs. > 11) for OS and DSS (p = 0.016 and p = 0.03, respectively), and at the cut-off point for 10 (< = 10 vs. > 10) for DFS (p = 0.033). For the NLN count, significant differences in survival were achieved for the cut-off point 5 (< = 5 vs. > 5) for OS and DSS (p = 0.0056 and p = 0.0045,) and the cut-off point 7 (< = 7 vs. > 7) for DFS (p = 0.029) (Fig. 2A, B, C). For LNR, significant differences in survival were shown for the cut-off point 0.4 (< = 0.4 vs. > 0.4) for OS (p = 0.019), for the cut-off point 0.3 (< = 0.3 vs. >0.3) for DFS (p = 0.049), and for the cut-off point 0.15 (< = 0.15 vs. > 0.15) for DSS (p = 0.042) (Fig. 2D, E, F). For LODDS, significant differences in survival were achieved for the cut-off point − 0.4 (<= -0.4 vs. > -0.4) for OS (p = 0.019), for the cut-off point − 1 (<= -1 vs > -1) for DFS (p = 0.048), and for the cut-off point − 1.6 (<= -1.6 vs. > -1.6) for DSS (p = 0.028) (Fig. 2G, H, I).

Single-factor analysis of survival

No effect of comorbidities on survival was observed, both with regard to separate analysis, and that based on CCI. However, an adverse effect on OS of the use of such medication as ACEIs (p < 0.0001) (Fig. 3A), calcium channel blockers (p = 0.027) and metformin (p = 0.021) was shown in the log-rank test. Our analysis also revealed that OS was adversely affected by the occurrence of complications, regardless of the degree in the Clavien-Dindo classification (p = 0.0087), occurrence of AL (p = 0.0026), and after dividing AL into early and late, by early AL (p < 0.0001). A positive effect on OS was shown with regard to adjuvant chemotherapy (p = 0.016), regardless of the number of cycles administered, and also chemotherapy > 3 cycles (p = 0.0016). Age > 65 years (p = 0.0045) was also a significant risk factor for OS.

A negative effect of the use of ACEIs (p = 0.04) (Fig. 3B) and metformin (p = 0.048), and a positive effect of the use of ARBs (p = 0.042) (Fig. 3D) on DFS was shown. In addition, a negative effect of the occurrence of complications, regardless of the degree in the Clavien-Dindo classification (p = 0.012), occurrence of AL (p = 0.024), and after dividing AL into early and late, of early AL (p = 0.0095) on DFS was shown. Histological grade G3 (p = 0.02) and the presence of PNI (p = 0.00015) had a negative effect on DFS, as well.

The DSS analysis showed an adverse effect of the use of ACEIs (p = 0.003) (Fig. 3C), metformin (p = 0.016), occurrence of complications, regardless of the degree in the Clavien-Dindo classification (p = 0.025), occurrence of AL (p = 0.0049), and after dividing AL into early and late, of early AL (p = 0.00027), and histological grade G3 (p = 0.018). No effect of other analysed factors on survival was revealed.

Multiple factor Cox analysis

The results of multiple factor Cox analysis are shown in Table 2. It was shown that factors having a negative effect on OS were: the use of ACEIs (HR: 3.059, 95% CI: 1.349–6.934, p = 0.007) and receiving < = 3 cycles of adjuvant chemotherapy (HR: 2.833, 95% CI: 1.289–6.229, p = 0.01). For DFS, significant adverse factors were: the use of ACEIs (HR: 3.11, 95%CI: 1.01–9.56, p = 0.047), presence of PNI (HR: 7.27, 95% CI: 2.74–19.3, p < 0.001), and the occurrence of postoperative complications (HR: 6.79, 95% CI: 2.09–22.11, p = 0.001). And a positive factor was the NLN count > 7 (HR: 0.33, 95% CI: 0.12–0.88, p = 0.026). In the DSS analysis, an adverse factor was the use of ACEIs (HR: 4.275, 95% CI: 1.44-12.694, p = 0.009), while a positive effect was caused by NLN > 5 (HR: 0.22, 95% CI: 0.082–0.586, p = 0.002). The other analysed factors were not significant in the multiple factor analysis.

Table 2
Multiple factor Cox regression model

Variables	HR	95% CI	p
OS			
Age > 65 years	2.05	0.95–4.43	0.069
CCI	0.93	0.39–2.22	0.865
Metformin	0.90	0.21–3.84	0.891
ACEIs	3.06	1.35–6.93	0.007
Calcium channel blockers	1.80	0.66–4.95	0.252
NLN > 5	0.45	0.19–1.10	0.080
LNR > 0.4	1.05	0.44–2.55	0.910
PLN > 11	1.69	0.41–6.95	0.468
Complications	2.01	0.70–5.71	0.192
Adj CT < = 3cycles	2.83	1.29–6.23	0.010
DFS			
Metformin	0.85	0.22–3.26	0.808
ACEIs	3.11	1.01–9.56	0.047
PLN > 10	0.76	0.20–2.95	0.692
LNR > 0.3	1.20	0.25–5.84	0.821
LODDS > -1	1.25	0.29–5.51	0.766
NLN > 7	0.33	0.12–0.88	*0.026*
Complications	6.79	2.09–22.11	0.001
ypG 3	0.75	0.13–4.21	0.748
PNI	7.27	2.74–19.30	< 0.001
DSS			
NLN > 5	0.22	0.08–0.59	0.002
LODDS > -1,6	0.97	0.12–7.98	0.975

HR- hazard ratio, CI- confidence interval, OS- overall survival, DFS- disease-free survival, DSS- disease-specific survival, CCI- Charlson comorbidity index, ACEIs- angiotensin-converting enzyme inhibitors, PLN- positive lymph nodes, NLN- negative lymph nodes, LNR- lymph node ratio, LODDS- log odds of positive lymph nodes, G- histological tumour grade, PNI- perineural invasion, Adj CT- adjuvant chemotherapy

Variables	HR	95% CI	p
LNR > 0.15	1.15	0.13–10.19	0.899
PLN > 11	2.65	0.45–15.44	0.280
Metformin	1.42	0.32–6.22	0.644
ACEIs	4.28	1.44–12.69	0.009
Complications	2.18	0.47–10.07	0.317
ypG 3	2.82	0.69–11.52	0.149

HR- hazard ratio, CI- confidence interval, OS- overall survival, DFS- disease-free survival, DSS- disease-specific survival, CCI- Charlson comorbidity index, ACEIs- angiotensin-converting enzyme inhibitors, PLN- positive lymph nodes, NLN- negative lymph nodes, LNR- lymph node ratio, LODDS- log odds of positive lymph nodes, G- histological tumour grade, PNI- perineural invasion, Adj CT- adjuvant chemotherapy

Discussion

Reports on the effect of AL on long-term survival are not consistent. [7, 10] The negative effect of early AL on survival shown in the single-factor analysis was not confirmed by the multiple factor Cox analysis. We have shown, however, a negative effect of postoperative complications on DFS, regardless of the degree in the Clavien-Dindo classification. Similar conclusions were drawn by Sprenger et al, who showed that the occurrence of any surgical complications (anastomotic leakage and/or abnormal wound healing) had a significant negative effect on OS and local recurrence free survival among the patients of the German Rectal Cancer Trial, as shown by a multiple factor analysis. [11] Possible mechanisms underlying the effect of complications on long-term oncological outcomes include no or delayed adjuvant therapy. [12] In a post hoc analysis we showed that the patients with complications significantly more often failed to receive > 3 cycles of adjuvant chemotherapy, which could suggest that such a claim is correct. In a multiple factor analysis, however, we confirmed the reports of no positive effect on DFS and DSS of adjuvant fluoropyrimidine-based chemotherapy used in the analysed period. [13, 14] On the other hand, we showed its positive effect on OS in the case of at least 4 full cycles.

ACEIs and ARBs are widely used medications in the treatment of arterial hypertension. Their basic mechanism of action is to block the renin-angiotensin system, which, through AT1 receptor, directly causes vasoconstriction and sodium reabsorption in the renal proximal tubule, and, through AT2 receptor, stimulates aldosterone secretion from the adrenal cortex. [15] It was observed that the use of these medications may reduce the risk of certain neoplasms, and also have a positive effect on neoplasm treatment outcomes. The mechanism of such action includes inhibition of At1-induced angiogenesis and modulation of the immune system in the tumour environment. Expression of RAS components was revealed in all types of cells in the neoplastic tumour microenvironment. [16] At the same time, however, ACEIs show an effect on the kallikrein-kinin system (KKS), inhibiting the process of kinin degradation to inactive peptides. Thus, the use of ACEIs, unlike of ARBs, results in an increased concentration of kinins,

which are considered to be pro-tumour peptides. [17] A murine model has revealed that human colorectal cancer cell lines show high expression of both types of bradykinin receptors (B1R and B2R), and their block results in tumour volume reduction, increased apoptosis and inhibition of angiogenesis in vivo. [18] Due to two-way activity of ACEIs, their antitumour effect related to the impact on RAS may be diminished by the impact on KKS.

There are few reports on the effect of ACEIs or ARBs on treatment outcomes in patients with rectal cancer. Typically, publications discuss subjects with colorectal cancer. Additionally, the effect of both these groups of medications is assessed jointly, which may significantly affect the results and cause conflicting conclusions. A few population studies and the latest meta-analysis have shown a protective effect of ACEIs/ARBs on the development of colorectal cancer. [19, 20] There are also reports, however, of no such correlation[21], or, in the case of a more detailed analysis, limitation of its influence only to ACEIs in the group aged below 65 years, with significant intensity of the protective effect in the proximal colon. [22] The effect of these drugs on the rectal cancer response to neoadjuvant treatment is unclear, too. Morris et al. showed that the use of ACEIs/ARBs significantly increases the frequency of complete responses after preoperative radiotherapy in a multiple factor analysis, [6] while Rombouts et al. did not confirm in their study a positive effect of these drugs. [23] Similar discrepancies exist regarding the assessment of the ACEIs/ARBs effect on long-term survival. Ozawa et al. showed a positive effect of ACEIs/ARBs on DFS in the course of left-sided colorectal cancer and stage I cancer. [24] Most authors, however, did not show an effect of these drugs on long-term oncological outcomes. [6, 25, 26] In the group of patients receiving ARBs, we achieved significantly better DFS as compared with patients who did not receive ARBs, including those receiving ACEIs. This parameter, however, was not significant in the multiple factor Cox analysis, most probably due to a small number of patients receiving ARBs. We have shown a negative effect of ACEIs on survival both in single- and multiple factor analysis, without showing an effect of comorbidities, analysed both separately and based on CCI. To the best of our knowledge, the effect of ACEIs has not been assessed so far exclusively in the group of subjects with ypN + rectal cancer. The analysis results point to a need of further studies in this group of patients. Taking into account a different effect of ACEIs and ARBs on long-term oncological outcomes, despite the fact that both these groups of drugs block RAS, it seems reasonable to analyse the effect of these drugs separately. Such approach seems to be justified also because of their different mechanisms of action, including no direct effect of ARBs on KKS.

We have not shown an effect of LNY on survival. Therefore, no understaging occurred in the study group, regardless of the LNY value. The results of our analysis seem to confirm the hypothesis of low LNY being the result of response to neoadjuvant therapy, instead of improper surgical or histopathological technique. [4, 27] We have also revealed no differences in survival for nodal staging according to the TNM classification (ypN1 vs ypN2), while the differences in survival based on PLN count were only observed at > 10, i.e. much above the N1/N2 threshold in the TNM classification. Nevertheless, the differences turned out to be insignificant in the multiple factor analysis, which may indicate a lack of effect of the PLN count on the prognosis in the study group of patients. The multiple factor analysis has also shown no significant effect of the LNR and LODDS parameters, which account for the PLN count.

The only parameter related to lymph nodes which in our analysis had a significant effect on survival was the NLN count in the surgical specimen, which is confirmed by observations of several authors. [3, 28] There have been promising attempts, yet requiring validation, to modify the current AJCC classification by adding the NLN count parameter. [29] This effect is explained by some authors by the presence of small (up to 2 mm) lymph nodes containing micrometastases which are not detected in standard HE staining and for that reason are assessed as NLN by pathologists. It is believed that an increased NLN count may reduce the risk of their non-removal, and, as a result, disease relapse. [30] Another possible explanation is an increase in the NLN count resulting from a stronger immune response to the tumour, with accompanying reactive lymph node enlargement. This phenomenon has a positive prognostic value and facilitates finding a higher number of lymph nodes in the specimen. [31, 32]

The analysis has typical limitations of retrospective and single-centre analyses. The neoadjuvant treatment was not performed with the use of a uniform schedule. However, we have shown no effect of this factor on the treatment outcomes. Data on comorbidities and medications taken were obtained from internal and anaesthesiological consultation records prior to surgery. It was not possible to assess the duration of using the medications.

Conclusions

The use of ACEIs may have a negative effect on long-term treatment outcomes in patients with ypN + M0 rectal cancer. In this group of patients, the NLN count seems to be an important prognostic factor, as well.

List Of Abbreviations

ACEIs- angiotensin-converting enzyme inhibitors

AL- anastomotic leakage

AR- anterior resection

ARBs- angiotensin receptor blockers

BMI- body mass index

CAD- coronary artery disease

CCI- Charlson comorbidity index

CRT- chemoradiotherapy

CI- confidence interval

DFS- disease-free survival

DIAB- diabetes mellitus

DSS- disease-specific survival

ENE- extranodal extension

G- histological tumour grade

HR- hazard ratio

KKS- kallikrein-kinin system

LNR- lymph node ratio

LNY- lymph node yield

LODDS- log odds of positive lymph nodes

LVI- lymphovascular invasion

NLN- negative lymph node

OS- overall survival

PLN- positive lymph node

PNI- perineural invasion

RAS- renin-angiotensin system

RASI- renin-angiotensin system inhibitors

RT- radiotherapy

SD- standard deviation

TRG- tumour regression grade

Declarations

Ethics approval and consent to participate

This retrospective study involving human participants was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by the institutional ethics committee of National Research Institute of Oncology (KB/430-53/19). Due to the retrospective design of the study, the ethics committee confirmed that informed consent was not necessary from participants.

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (Additional file 1).

Competing interests

The authors declare that they have no competing interests

Funding

The authors have no financial or non-financial support to disclose

Author's contributions

MZ created the work concept and design, MZ, WS, PS, GH, DAW and DŻ participated in data collection, MZ and WS participated in data analysis and interpretation, MZ wrote the manuscript, AC substantively revised the manuscript. All authors have read and approved the manuscript.

Acknowledgements

Not applicable

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Figures

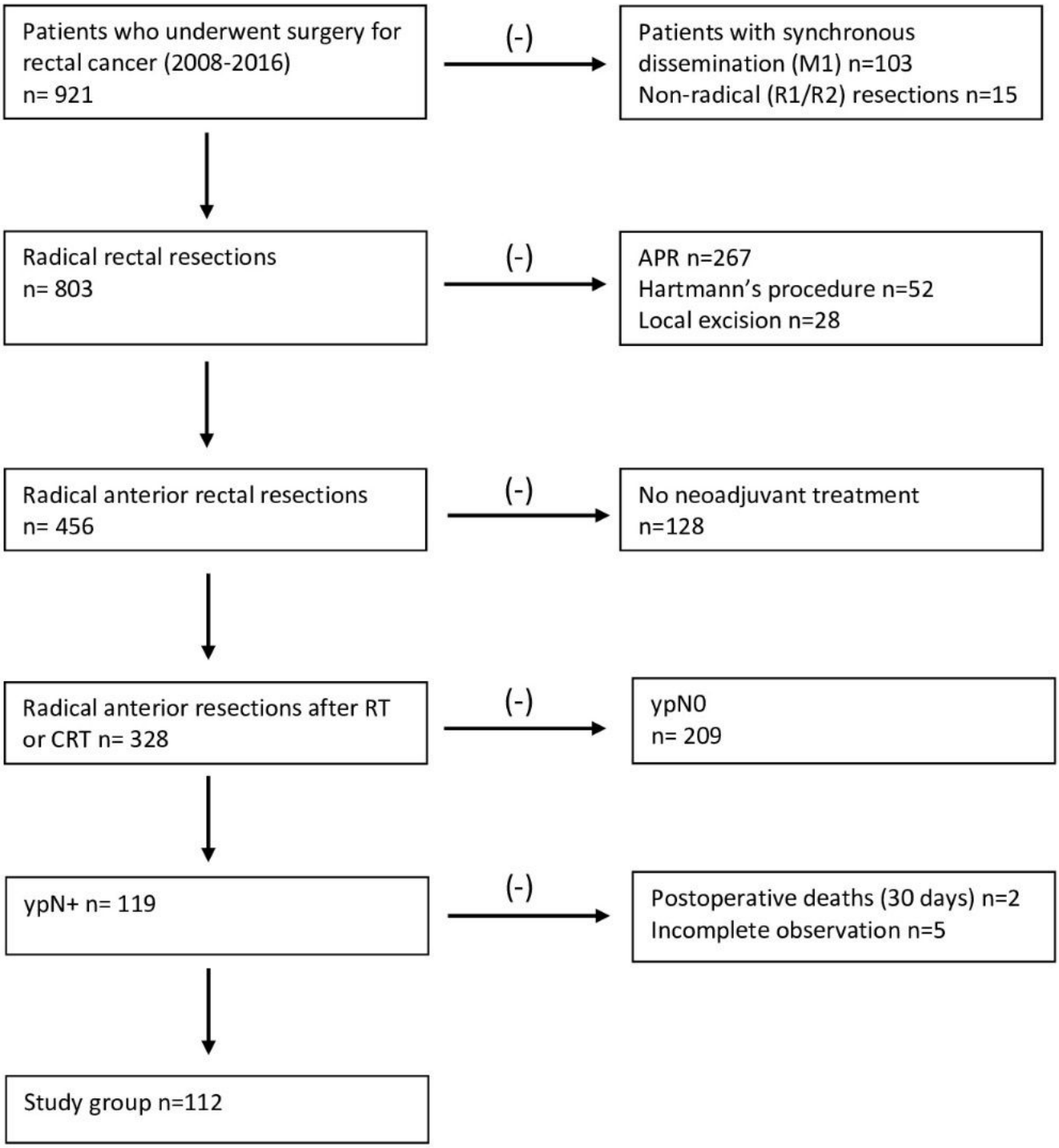

Figure 1

Process of study group formation

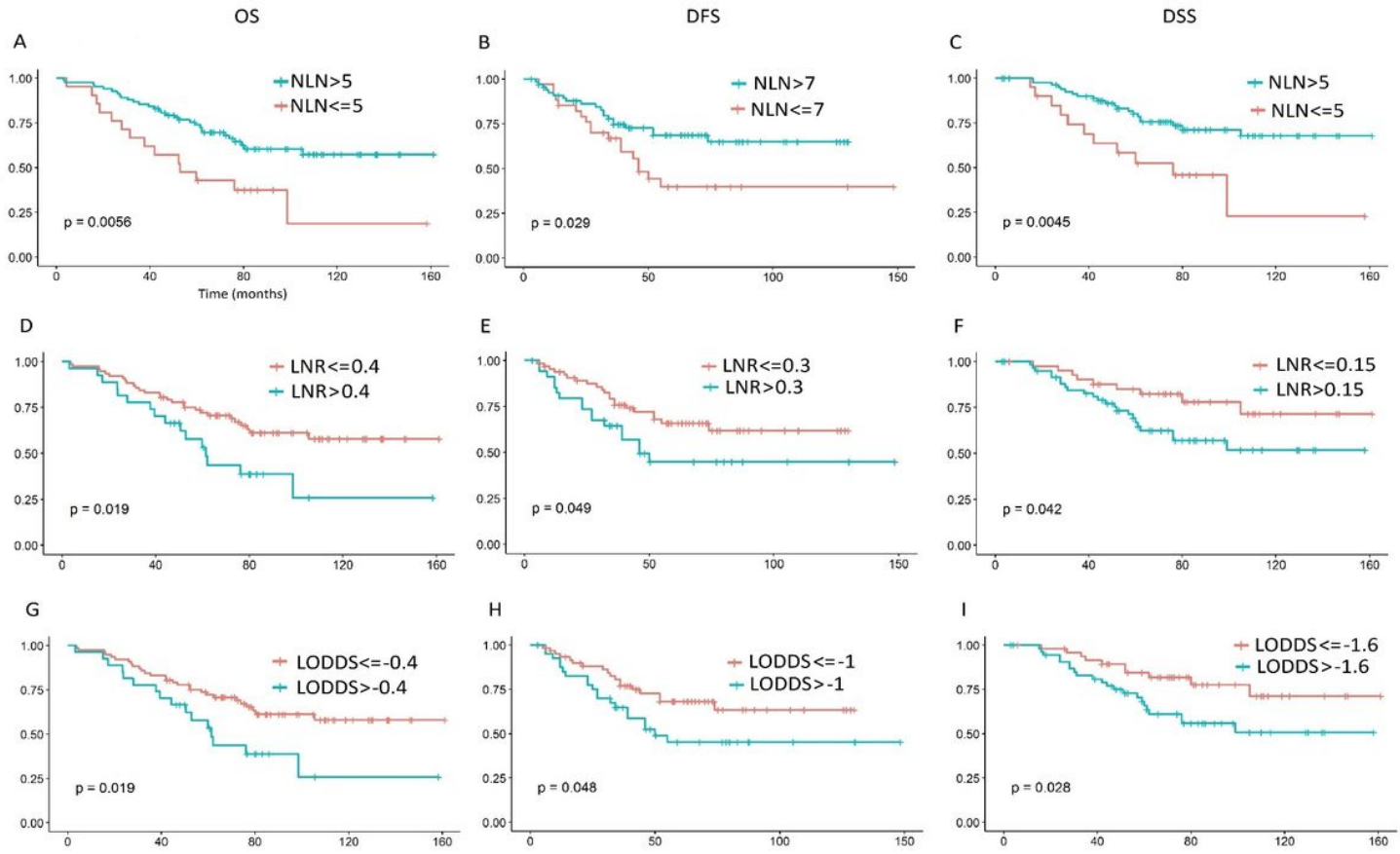

Figure 2

Survival analysis (OS, DFS and DSS) depending on negative lymph node count (A-C), lymph node ratio (D-F) and log odds of positive lymph nodes (G-I).

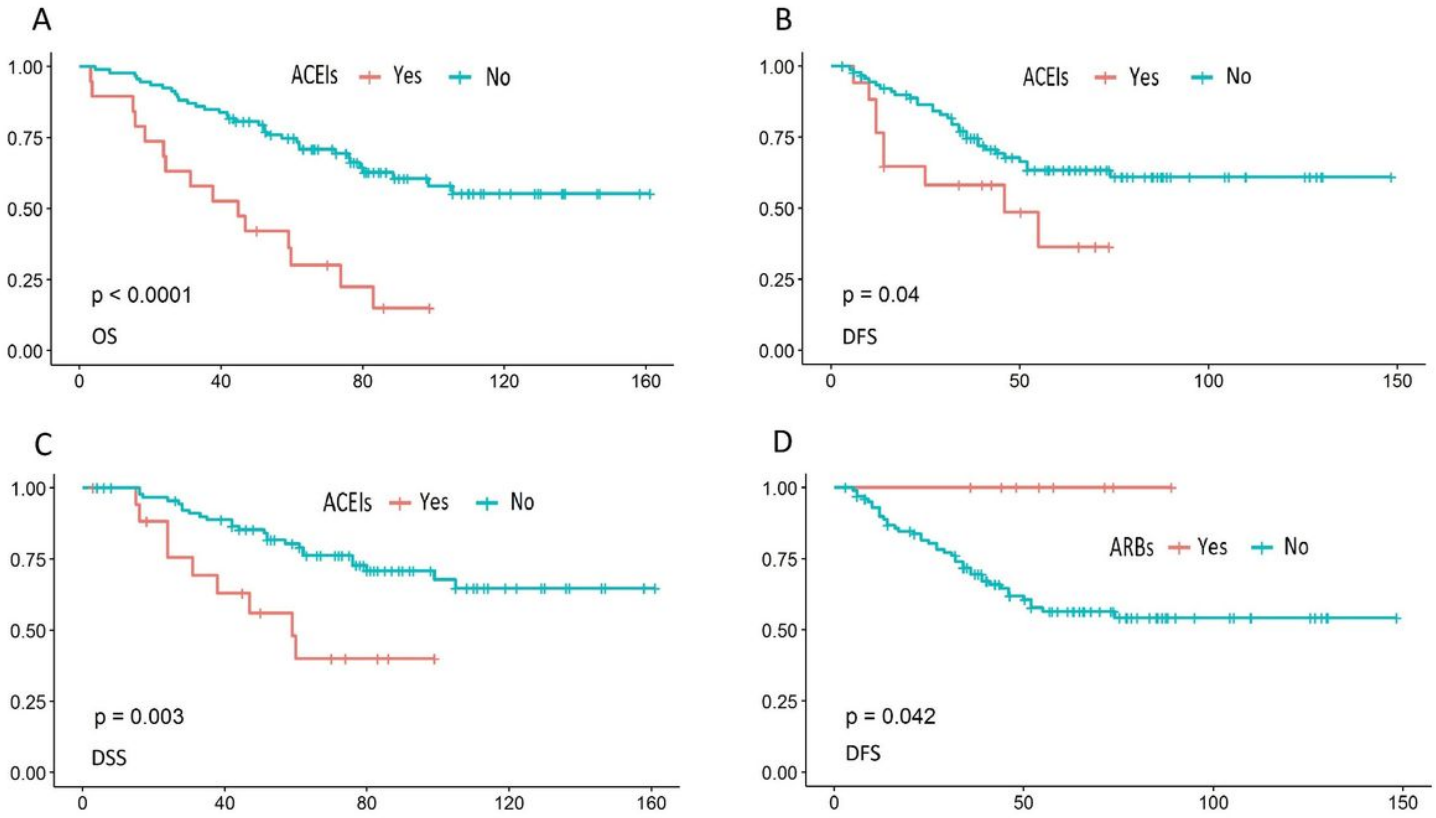

Figure 3

Survival analysis (OS, DFS and DSS) of patients depending on angiotensin-converting enzyme inhibitors (A-C) and DFS depending on angiotensin receptor blockers (D).

Supplementary Files

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- Supplementaryfile1dataset.xlsx