Type 2 Endoleak With or Without Intervention and Survival After Endovascular Aneurysm Repair

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WHAT THIS PAPER ADDS

A type 2 endoleak (T2EL) following endovascular aneurysm repair (EVAR) is associated with an increased need for secondary intervention and presumed risk of rupture, thus analysing the impact of an isolated T2EL on mortality is necessary. After an 11 year follow up, survival in patients who underwent a secondary intervention for T2EL was not better than those who were treated conservatively. Most importantly, this study highlights the need for a conservative approach and for high quality prospective studies to better understand the natural course of T2EL, and to guide the direction of their management.

Objective: The aims of the present study were to examine the impact of type 2 endoleaks (T2EL) on overall survival and to determine the need for secondary intervention after endovascular aneurysm repair (EVAR).

Methods: A multicentre retrospective cohort study in the Netherlands was conducted among patients with an infrarenal abdominal aortic aneurysm (AAA) who underwent EVAR between 2007 and 2012. The primary endpoint was overall survival for patients with (T2EL+) or without (T2EL-) a T2EL. Secondary endpoints were sac growth, AAA rupture, and secondary intervention. Kaplan—Meier survival and multivariable Cox regression analysis were used.

Results: A total of 2 018 patients were included. The median follow up was 62.1 (range 0.1 — 146.2) months. No difference in overall survival was found between T2EL+ ($n = 388$) and T2EL- patients ($n = 1630$) ($p = .54$). The overall survival estimates at five and 10 years were 73.3%/69.4% and 45.9%/44.1% for T2EL+/T2EL- patients, respectively. Eighty-five of 388 (21.9%) T2EL+ patients underwent a secondary intervention. There was no difference in overall survival between T2EL+ patients who underwent a secondary intervention and those who were treated conservatively ($p = .081$). Sac growth was observed in 89 T2EL+ patients and 44/89 patients (49.4%) underwent a secondary intervention. In 41/44 cases (93.1%), sac growth was still observed after the intervention, but was left untreated. Aneurysm rupture occurred in 4/388 T2EL patients. In Cox regression analysis, higher age, ASA classification, and maximum iliac diameter were significantly associated with worse overall survival.

Conclusion: No difference in overall survival was found between T2EL+ and T2EL- patients. Also, patients who underwent a secondary intervention did not have better survival compared with those who did not undergo a secondary intervention. This study reinforces the need for conservative treatment of an isolated T2EL and the importance of a prospective study to determine possible advantages of the intervention.

Keywords: Aortic aneurysm, Abdominal, Endoleak, Endovascular procedures

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INTRODUCTION

Endovascular aneurysm repair (EVAR) is a procedure used to repair an abdominal aortic aneurysm (AAA) in patients with suitable anatomy.[1] The advantages of EVAR include lower mortality risk, fewer complications, and a shorter length of hospital stay than open surgical repair.[2—4] However, EVAR can also entail graft related complications and subsequent interventions. The most prevalent indications for secondary intervention after EVAR are endoleaks.[5] Type 2 endoleaks (T2ELs) occur after EVAR in 16% — 50% of patients, and comprise approximately half of all endoleaks.[6—8] T2ELs appear when retrograde blood flow from aortic side branches pressurises the aneurysm sac.[9,10] Approximately 80% — 90% of T2ELs resolve spontaneously during follow up, but some do not.[11] Several studies suggest

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that a T2EL is a benign complication,[8,12] whereas others have associated T2EL with adverse late outcomes resulting in a high secondary intervention rate and significant risk of aneurysm related complications.[13] If there is a T2EL with aneurysm sac expansion, the 2019 European Society for Vascular Surgery (ESVS) guideline recommends imaging to rule out a type 1 or a type 3 endoleak.[14] Current guidelines recommend conservative treatment for T2EL; however, if the aneurysm sac increases by more than 10 mm, secondary intervention is recommended.[14]

The present study describes the experience with T2ELs after EVAR in 16 medical centres in the Netherlands over an 11 year follow up period. Analysing the long term effects of T2ELs using a large dataset may lead to greater consensus about treatment protocols and may give direction to management of T2ELs.

MATERIALS AND METHODS

Study design and setting

This was a multicentre retrospective cohort study of all consecutive patients who underwent elective EVAR between January 2007 and January 2012 at 16 medical centres in the Netherlands. Both academic and teaching hospitals were included. This study was carried out in accordance with the STROBE statement,[15] and was approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location Academic Medical Centre, Amsterdam, the Netherlands. The opt out recruitment method was used, which gave potential participants the option to object to participation within four weeks. The Medical Research Involving Human Subject Act (WMO) did not apply to this study. This was confirmed by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location Amsterdam Medical Centre. This study was conducted according to the General Data Protection Regulation (AVG 2016). All medical files were reviewed by two independent reviewers (SM, AG). Data were stored and analysed anonymously.

Participants

Data from 2 279 patients who underwent elective EVAR without chimneys or fenestrations between 2007 and 2012 were collected retrospectively and recorded in a database. The criterion for inclusion in the study was surgery for an asymptomatic or symptomatic non-ruptured infrarenal aortic or aorto-iliac aneurysm. The study excluded patients with ruptured aneurysms, isolated iliac aneurysms, and patients with a type 1, 3, or 4 endoleak. If patients had T2EL detected during follow up, but another endoleak (type 1, 3, or 4) before rupture, these patients were excluded. Also, those who did not undergo computed tomography angiography (CTA) scanning within 90 days after the initial operation were excluded.

Data collection

Data were collected from patient medical records and included the following baseline and anatomical variables: age, sex, pre-operative AAA diameter, ASA classification, type of endograft, neck length, and maximum iliac artery diameters. Patients were divided into two groups: with or without T2EL (T2EL+ and T2EL-).

Endpoints

The primary endpoint was overall survival for T2EL+ and T2EL- patients. Secondary endpoints were secondary interventions, aneurysm sac growth, and rupture. Mortality data were ascertained by record linkage between the study population and the Netherlands national causes of death register.

Definitions

An isolated T2EL was defined as a T2EL without signs of any additional endoleak during the follow up period and was subdivided into two groups: early and late onset. An early onset of T2EL was diagnosed at the first post-operative CTA within 90 days of the primary procedure, and a late onset T2EL was one identified subsequent to the initial post-operative CTA. Sac growth was defined as aneurysm sac diameter growth of $\geq$5 mm compared with the most recent follow up imaging, or as a change in sac diameter of $>$5 mm when compared with the first post-operative AAA diameter.[16] Each centre followed their local surveillance protocol (Table S1). Secondary intervention was defined as any additional procedure performed during follow up, for an aneurysm related complication, that was required following, and related to, the initial aortic repair. Secondary interventions were divided into two groups: endovascular and open approaches. The 30 day mortality was defined as death from any cause within 30 days after EVAR. All cause mortality was expressed as all deaths that occurred in the study population during the follow up period, regardless of cause.

Statistical analysis

Nominal variables are presented in numbers (%) and continuous variables as mean and standard deviation (SD), or median and interquartile range (IQR) depending on whether they followed a normal distribution. The Shapiro–Wilk test was used to assess normality. Patients were grouped according to the presence or absence of T2EL. Demographic and clinical characteristics were compared between T2EL+ and T2EL- groups by chi square or Fisher's exact tests as appropriate for nominal variables, whereas continuous variables were compared between the two groups by the independent sample *t* test or Mann–Whitney *U* test, depending on the distribution. Survival analysis was

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Table 1. Baseline characteristics of patients with infrarenal abdominal aortic aneurysm (AAA) who underwent endovascular aneurysm repair between 2007 and 2012

Characteristics	Missing values	Type 2 endoleak (n = 388; 19.2%)	No endoleak (n = 1 630; 80.8%)	p value
Male sex	0	331 (85.3)	1470 (90.2)	.004
Age − y	0	74.8 ± 10.8	74.9 ± 9.9	.86
AAA diameter − cm	3	6.0 ± 1.0	6.0 ± 1.3	.44
ASA classification	0			.54
ASA I		4 (1.0)	14 (0.9)	
ASA II		164 (42.3)	651 (40.0)	
ASA III		201 (51.8)	848 (52.0)	
ASA IV		18 (4.6)	110 (6.7)	
ASA V		1 (0.3)	2 (0.1)	
Unknown		0	5 (0.3)	
Endograft	0			<.001
Zenith Flex; Cook		132 (34.0)	589 (36.1)	
Endurant; Medtronic		115 (29.6)	620 (38.0)	
Excluder; Gore		72 (18.6)	188 (11.5)	
Talent; Medtronic		31 (8.0)	99 (6.1)	
Powerlink; Endologix		5 (1.3)	6 (0.4)	
Anaconda; Vascutek		2 (0.5)	6 (0.4)	
Aptus; Aptus endosystems		7 (1.8)	6 (0.4)	
Other		1 (0.3)	8 (0.5)	
Unknown		23 (5.9)	108 (6.6)	
Neck length − cm	599	3.0 ± 2.6	3 ± 1.6	.31
Maximum iliac diameter − cm	765	1.9 ± 1.9	1.7 ± 3.3	.41

Data are presented as n (%) or mean ± standard deviation. ASA = American Society of Anesthesiologists.

performed by the Kaplan—Meier method, and the log rank test was used to compare subgroups. Univariable and multivariable analyses were performed using Cox regression analysis to identify independent factors associated with overall survival. Only variables with a p value < .2 on univariable analysis were entered into the multivariable Cox regression model. Variables entered into the models included age, sex, pre-operative AAA diameter, ASA classification, endograft type, neck length, largest maximum diameter of both iliac arteries, and sac growth. Complete case analysis was performed in the regression analysis. To check the violation of the proportionality hazard assumption, a log-log plot for the hazard ratio over time was performed. Multiple imputation by predictive mean matching (PMM) based on 10 imputation sets was used as a sensitivity analysis to account for missing baseline variables. The threshold for statistical significance was set at a p value ≤ .05. All statistical analyses were performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline demographics and clinical characteristics

From 2007 to 2012, 2 279 patients underwent EVAR. After applying the exclusion criteria, a total of 2 018 patients were included for analysis. The mean (SD) age at EVAR was 74.9 years (10.1) and the majority of patients were male (89.2%). Baseline demographics and clinical characteristics stratified by T2EL status are listed in Table 1. No endoleak was identified in 1 630 patients (80.8%), and an isolated T2EL was found in 388 patients (19.2%). The median follow up duration was 62.1 months (IQR 59.9; range 1.2 — 146.2) in the T2EL+ group, and 59.7 months (IQR 61.7; 0.1 — 143.9) in the T2EL- group.

Outcome

The 30 day mortality for the study cohort was 1.3% (26/2 018). The overall survival estimates were 95.1%, 73.3%, and 45.9% at 1, 5, and 10 years, respectively, for T2EL+ patients and 92.5%, 69.4%, and 44.1%, respectively, for T2EL-

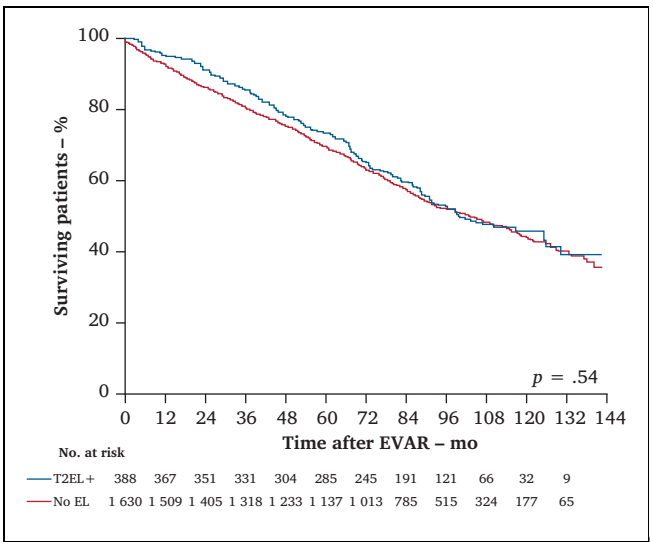

Figure 1. Cumulative Kaplan—Meier estimate of effect of type 2 endoleak (T2EL) on overall survival of 2018 patients with endovascular aneurysm repair (EVAR). Survival did not differ between those with or without a T2EL (p = .54, log rank test).

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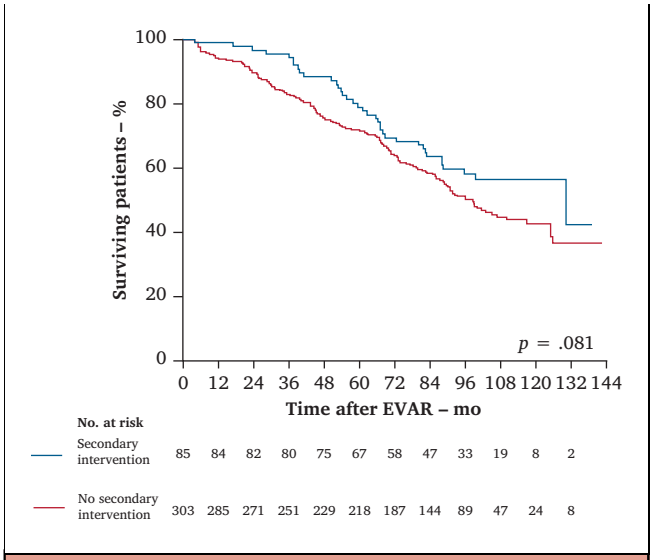

Figure 2. Cumulative Kaplan–Meier estimate of effect of secondary intervention on overall survival after endovascular aneurysm repair (EVAR) in subgroup of 388 patients with type 2 endoleak (T2EL). Survival did not differ between those with or without intervention for T2EL ($p = .081$, log rank test).

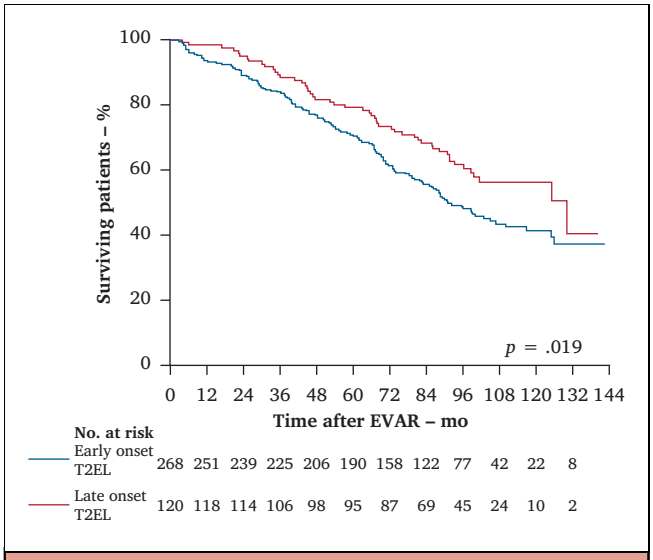

Figure 3. Cumulative Kaplan–Meier estimate of effect of early and late onset type 2 endoleak (T2EL) after endovascular aneurysm repair (EVAR) on overall survival of 388 T2EL+ patients. Survival was worse for early onset T2EL patients ($p = .019$, log rank test).

patients. Overall survival did not differ between the groups ($p = .54$) (Fig. 1). This was also confirmed by multivariable analysis. In total 197/388 (50.9%) patients in the T2EL+ group died and 857/1 630 (52.6%) in the T2EL- group died ($p = .55$). In addition, there was no difference in overall survival between T2EL+ patients who had a secondary intervention for T2EL, and those who did not ($p = .081$) (Fig. 2). The median follow up duration in the T2EL+ group who underwent a secondary intervention was 63.8 (IQR 47.5; range 2.0 — 135.5) months, and 59.6 (IQR 63.5; range 1.2 — 146.2) months in the T2EL+ group who did not undergo a secondary intervention. When comparing the T2EL+ and T2EL- groups: age, ASA classification, type of endograft, AAA diameter, neck angulation, maximum iliac diameter, and sac growth were independently associated with death in univariable analysis. In multivariable Cox regression analysis, age, ASA classification, and the maximum diameter of iliac arteries remained statistically significantly associated with death (Table 2). The Cox proportional hazard assumption was met (Appendix S2, supporting information).

Type 2 endoleak characteristics

A total of 388 patients with an isolated T2EL were further categorised as early or late onset T2EL. Two hundred and sixty-eight patients developed an early T2EL and 120 a late

Table 2. Univariable and multivariable analysis of patients with or without type 2 endoleak after endovascular repair of infrarenal abdominal aortic aneurysm (AAA)

	Univariable analysis Hazard ratio (95% CI)	Multivariable analysis Hazard ratio (95% CI)
Age — y *	1.069 (1.060–1.078)	1.069 (1.057–1.081)
ASA classification		
ASA I/II (1) *	Reference	Reference
ASA III (2)	1.223 (1.074–1.392)	1.311 (1.109–1.550)
ASA IV/V (3)	1.959 (1.557–2.465)	1.854 (1.390–2.472)
Endograft		
Zenith Flex (Cook) (1)	Reference	
Talent (Medtronic) (2)	1.004 (0.788–1.279)	
Endurant (Medtronic) (3)	0.801 (0.604–1.062)	
Excluder (Gore) (4)	0.920 (0.723–1.171)	
Other (5)	0.947 (0.700–1.282)	
AAA diameter — cm	1.128 (1.065–1.195)	
Maximum iliac diameter — cm *	1.170 (1.083–1.264)	1.018 (1.012–1.024)
Sac growth	0.944 (0.753–1.185)	

ASA = American Society of Anesthesiologists; CI = confidence interval.
* Variables significantly related to mortality in multivariable analysis.

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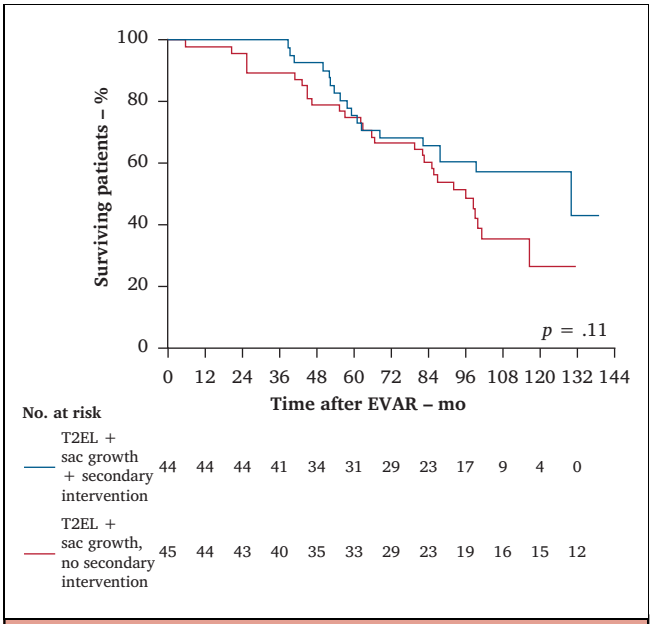

Figure 4. Cumulative Kaplan–Meier estimate of effect of sac growth on overall survival stratified by secondary intervention status for 89 patients with type 2 endoleak (T2EL) and sac growth after endovascular aneurysm repair (EVAR). Survival did not differ between those T2EL patients with sac growth with or without intervention ($p = .11$, log rank test).

T2EL. The mean age (SD) of the early onset T2EL group was 74.4 years (7.7) compared with 72.6 (8.5) years in the late onset T2EL group ($p = .039$). Most of the early onset T2EL cases were resolved by the end of follow up (197/268, 74.0%). In the late onset T2EL group, 85/120 (71.0%) of cases had resolved by the end of follow up. In addition, fewer interventions were performed in the early onset T2EL group 44/268 (16.4%) than in the late onset T2EL group 41/120 (34.2%). Survival of patients with early onset T2EL was worse than that of patients with a late onset T2EL ($p = .019$) (Fig. 3). Sac growth was identified in 49/268 (18.0%) patients in the early onset T2EL group and in 40/120 (33.0%) patients in the late onset T2EL group. One aneurysm rupture was observed in the early onset T2EL group, and three in the late onset T2EL group.

Secondary interventions

Secondary interventions were undertaken in 249 of 2 018 patients. A total of 223 patients (11.1%) underwent one secondary intervention, and 26 (1.3%) underwent multiple interventions. Eighty-five of 388 (22.0%) patients in the T2EL+ group underwent a secondary intervention compared with 164 of 1 630 (10.0%) patients in the T2EL- group ($p < .001$). The median time to secondary intervention in the T2EL+ group was 32.3 months (IQR 38.1; range 0.1 — 130.3) and in the T2EL- group 12.8 months (IQR 48.0; range 0.03 — 141.7). In 55 of the 85 T2EL+ patients, an endoleak was the indication for the secondary intervention. In the remaining 303 of 388 T2EL+ patients the T2EL was managed conservatively. In 221/303 (72.9%) cases the T2EL had spontaneously resolved by the end of follow up, and in 56 patients a recurrent endoleak was identified.

Sac growth

Sac growth was observed in 152/2 018 (7.5%) patients. Sac growth was seen in 89/388 (23%) T2EL+patients compared with 63/1 630 (3.9%) of T2EL- patients ($p < .001$). Forty-four T2EL+ patients with sac growth underwent a secondary intervention. In 41/44 patients (93.2%) sac growth continued after secondary intervention but was left untreated. Survival analysis in the subgroup of patients with sac growth showed that there was no difference in overall survival for patients who did or who did not undergo a secondary intervention ($p = .11$) (Fig. 4).

Ruptures

The number of aneurysm ruptures in the study cohort was 17/2 018 (0.8%). Aneurysm rupture occurred in four of 388 (1.0%) T2EL+ patients, of whom three patients had sac growth. In two patients it was decided not to intervene and to provide palliative care, and in two cases surgical treatment was performed. One patient was treated successfully by endovascular repair and one patient was treated unsuccessfully by open repair and died within 24 hours after surgery. Ruptures occurred within 18.5 — 130.3 months after EVAR. The median time to rupture was 64.8 months (IQR 59.7; range 18.5 — 130.3) for the entire cohort. The mean (SD) aneurysm diameter at time of rupture was 7.1 cm (1.7). In patients with AAA rupture the overall mortality was 11/17 (64.7%).

DISCUSSION

This study has highlighted ongoing uncertainties in management of T2ELs and aimed to investigate both the impact of T2EL on overall survival and the need for intervention after T2EL. Important findings regarding T2EL after EVAR were examined in further detail: 1) the incidence of an isolated T2EL in the present study was 17%, 2) no difference in overall survival was identified between patients with or without a T2EL, and no difference in overall survival was observed between patients with a T2EL who underwent a secondary intervention and those who did not undergo secondary intervention, 3) survival in patients with an early onset T2EL was worse than that of patients with a late onset T2EL.

The incidence of T2ELs in the present study was consistent with the incidence in previously published articles.[8,17,18] Patients in the present cohort were followed for a median of 62.1 months (IQR 59.9; range 0.1 — 146.2), which was longer than other studies in the same field.[13,16,18] Evidence suggests that T2EL might disappear spontaneously, and that in many other cases there is no aneurysm sac growth with its related risk of complications.[18] The present study showed aneurysm sac growth in 89 of 388 patients with an isolated T2EL, which is lower

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than in similar studies.[16] A possible explanation for this is that only patients with an isolated T2EL were included. Walker *et al.* also included patients with an additional endoleak (type 1,3,4) in this number. Although sac growth was identified in 22.9% of the T2EL patients, no difference in mortality was observed between T2EL+ and T2EL- patients during follow up. Similar findings were found in a multicentre EVAR registry, which stated that overall survival was unaffected by the presence of a type II endoleak.[16] This small difference in survival between T2EL+ and T2EL- patients might be explained as the group in which no endoleak was identified consisted of patients in whom other abnormalities were seen (outflow obstruction, endotension, endograft migration or endograft infection).

In this study, an isolated T2EL was found to be associated with a greater risk of sac growth and secondary intervention. This is in line with the recently published report of the ENGAGE registry, in which a significantly higher rate of secondary intervention was seen for T2EL+ patients.[8] Unfortunately, early intervention to prevent T2EL is rarely carried out and the main question of whether secondary intervention increases the chance of survival remains unanswered. In the present study, no difference in overall survival was demonstrated between T2EL+ patients who underwent a secondary intervention and those who did not. Secondary interventions tended to be unsuccessful in patients with aneurysm sac growth. These findings were consistent with previous studies showing that survival in patients who underwent a secondary intervention for sac growth was not better than in patients treated conservatively.[16,19] An important issue to address is that it might be possible that T2EL+ patients in this study are subject to secondary intervention for progressive loss of seal and not for fixing the endoleak. Unfortunately, the type of intervention could not be determined in the present study. Moreover, in the present study, in most cases sac growth was still present after the secondary intervention. A recent systematic review did not find any compelling evidence for the efficacy of secondary intervention for T2EL after EVAR, and in addition, found that sac growth was still common after secondary intervention.[20]

Several studies found T2ELs to follow a benign course,[13,21,22] whereas others reported an increased risk of rupture and death.[23,24] In the present study, T2EL had disappeared spontaneously in 11.0% ($n = 221$) of patients by the end of follow up, which was lower than the 17.6% reported in the study by Kim *et al.*[25] This difference might be attributed to that study reporting only on early onset T2EL patients. In total 17 ruptures were identified, four ruptures occurred in the T2EL+ group, of which one rupture was attributable to a T2EL alone. This is not in line with the study by Silverberg *et al.*, in which no ruptures were observed in a cohort of 154 T2EL patients.[26] Furthermore, the present study showed that late onset T2EL was less likely to have resolved spontaneously by the end of the follow up period than early onset T2EL. However, patients with an early onset T2EL were less likely to survive than patients with a late onset T2EL. This might be explained as patients in the early onset group were on average two years older than those in the late onset group. This was also seen in the survival curve in which the late endoleak group had a survival advantage of two years. Secondary intervention rates were higher in the late onset T2EL group. These findings were similar to those of previous studies.[5,27,28]

Another interesting observation is that the maximum diameter of the iliac arteries was associated with mortality, which has not been demonstrated in previous studies. The explanation of this observation remains unclear. The present authors hypothesise that this observation is mere coincidence.

The present authors recommend that in early onset T2EL cases, secondary intervention should be considered. Additionally, to better understand the natural course of T2EL, further research in the form of a prospective design is advisable. The 2019 ESVS guidelines advise a less strict follow up protocol in patients without an endoleak and a good seal, and yearly surveillance in the presence of an isolated T2EL.[14] Based on the present study, a less firm surveillance schedule might also be safe. If sac growth concomitant with a T2EL is present, imaging should be conducted to rule out other causes of growth like type I or III endoleak.[14]

There are some limitations to this study. First, as the diagnosis of a T2EL was based on radiology reports, the present study may suffer from information bias. It is possible that some endoleaks were incorrectly categorised or not detected at all. Diagnostic imaging plays a crucial role in detecting a T2EL. As CTA and DUS mainly detect large endoleaks, more sensitive imaging such as blood pool MRA may be necessary to detect occult T2ELs.[29] Furthermore, residual confounding is possible because of the retrospective nature of the study. Another limitation of this study was that some patients were lost to follow up as they were followed up in a non-participating hospital. In addition, because in many cases the cause of death was unknown, it was not possible to study the impact of a T2EL on aneurysm related mortality. Regardless of these limitations, understanding of the impact of T2EL on overall survival and the need for intervention has improved since the introduction of the present study, but prospective research on the natural course of T2ELs and its response to treatment is required to better understand their natural course.

Conclusion

This observational study showed that an isolated T2EL occurred in 17% of patients undergoing EVAR. It was found that an isolated T2EL had no impact on overall survival and that T2EL patients who underwent a secondary intervention did not have better survival compared with those who did not undergo a secondary intervention. These results reinforce the need for conservative treatment of an isolated

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T2EL and the importance of a prospective study to determine the possible advantages of intervention.

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.01.017.

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