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**Aggressive versus Symptom-guided Drainage of Malignant
Pleural Effusion via Indwelling Pleural Catheters:
*The Australasian Malignant PLeural Effusion (AMPLE)-2
randomized clinical trial***

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ABSTRACT

Background

Indwelling pleural catheter (IPC) is an established management option for malignant pleural effusion (MPE) and has advantages over talc slurry pleurodesis. The optimal regimen of drainage after IPC insertion remains debated and ranges from aggressive (daily) drainage to drainage only when symptomatic.

Methods

AMPLE-2 was an open-labelled, randomized trial that involved 11 centers in Australia, New Zealand, Hong Kong and Malaysia between July 2015 and January 2017 [ACTRN12615000963527]. Patients (n=87) with symptomatic MPEs were randomized (1:1) to the *Aggressive* (daily) or *Symptom-guided drainage* arms for 60 days and minimized by cancer type (mesothelioma vs others), performance status (ECOG 0-1 vs ≥ 2), presence of trapped lung and prior pleurodesis, and followed up for 6 months. The results were analyzed by an intention-to-treat approach.

Findings

The primary outcome compared the mean daily breathlessness scores of each patient, measured using a 100mm visual analogue scale (VAS), over the first 60 days and found no significant difference between the *Aggressive* and *Symptom-guided drainage* arms (geometric means=13.1 vs 17.3 mm respectively, $p=0.1766$, ratio of geometric means 1.32, 95% CI 0.88-1.97). More patients in the *Aggressive* arm developed spontaneous pleurodesis than in the *Symptom-guided* arm in the first 60 days (37.2% [16/43] vs 11.4% [5/44] respectively, $p=0.0049$) and at 6 months (44.2% [19/43] vs 15.9% [7/44] respectively, $p=0.0065$; HR=3.287 [95% CI 1.396-7.740]). Patient-reported quality-of-life measures, using EQ-5D-5L, were better in the *Aggressive* arm than in the *Symptom-guided* arm: estimated means 0.713 (95% CI 0.647-0.779) vs 0.601 (95% CI 0.536-0.667) respectively. The estimated difference in means was 0.112 (95% CI 0.0198-0.204), $p=0.0174$. There were no significant between-group differences in pain scores, total days spent in hospital or mortality. Serious adverse events occurred in 25.6% (11/43) and 27.3% (12/44) patients in the *Aggressive* and *Symptom-guided drainage* arms respectively, including 11 episodes of pleural infection in 9 patients (5 in the *Aggressive* arm and 6 in the *Symptom-guided drainage* arm).

Interpretation

No differences were found between the aggressive (daily) and the symptom-guided drainage regimens for IPC in providing breathlessness control. Patients managed with the two schedules did not differ on their pain scores, days spent in hospital or mortality. Daily IPC drainage is more effective in promoting spontaneous pleurodesis and may improve quality-of-life.

Funding

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INTRODUCTION

Malignant pleural effusion (MPE) can complicate most cancers.¹ The associated breathlessness is often distressing, debilitating, and significantly impairs quality-of-life (QoL).² MPE accounts for over 125,000 hospital admissions per year in the USA alone.³

Indwelling pleural catheter (IPC) is a new therapeutic approach for MPE and its advantages have been confirmed in recent randomized trials.^{4,5} Treatment with IPC significantly reduces days spent in hospital and the need for further invasive pleural procedures in patients' remaining life,⁴ compared with conventional talc slurry pleurodesis, while offering the same level of symptom and QoL improvement.^{4,5} IPC is increasingly adopted worldwide as the first line management for MPE.

The logical next goal is to optimize the use of IPC and hence its benefits. Few data exist to guide drainage approaches for IPC patients. Practices vary worldwide, ranging from aggressive (daily or alternate day) drainage, often used in North American centers,⁶ to drainage only when symptoms develop which is common in the rest of the world. These differences in practice may potentially influence outcome and complication rates.

Aggressive daily drainage arguably keeps the pleural space dry and provides best symptom control everyday whereas those who advocate symptom-guided drainage contend that the goal of MPE care is palliation and drainage of IPC is only indicated when symptoms arise. The symptom-guided approach may reduce a significant amount of burden and consumable costs compared with daily drainages, and may reduce the risk of iatrogenic introduction of pleural infection.

On the other hand, it is believed that frequent IPC drainage may facilitate approximation of the visceral and parietal pleura and facilitate their symphysis ('spontaneous' pleurodesis), and allow removal of the catheter. Daily drainage has been shown to promote pleurodesis more effectively than alternative day drainage.⁶ Whether a symptom-guided approach affects the rate of pleurodesis is unknown.

The Australasian Malignant Pleural Effusion (AMPLE) Trial-2 was a multi-centered, open-labelled, randomized clinical trial (RCT) designed to address the equipoise between *Aggressive*

(daily) versus *Symptom-guided* approaches to IPC drainage in patients with a MPE, specifically their efficacy in breathlessness control, induction of pleurodesis, improvement of QoL and the associated hospitalization and complication rates.⁷

METHODS

The study was a randomized, multicenter, open-label trial. Study participants were enrolled (see published study protocol⁷) from 11 centers: Sir Charles Gairdner, Fiona Stanley, Royal Perth, Saint John of God Bunbury, Sunshine Coast University, Royal Adelaide, Wesley, and St George & The Sutherland Hospitals in Australia; Middlemore Hospital in New Zealand; Queen Elizabeth Hospital, Kota Kinabalu, in Malaysia; and Queen Mary Hospital Hong Kong. Ethics and governance approvals were obtained from the human research ethics committee at all sites, the primary committee being the Sir Charles Gairdner and Osborne Park Health Care Group Human Research and Ethics Committee (2014-079). Written, informed consent was obtained from all participants.

Eligibility: All participants enrolled were adults who required IPC placement for management of a MPE. All participants had malignant cells identified in the pleural fluid or pleural biopsy tissue; or a large exudative pleural effusion without other causes in a patient with known disseminated extra-pleural malignancy. Exclusion criteria included age <18 years, expected survival <3 months, pleural infection, chylothorax, pregnancy, lactation, un-correctable bleeding diathesis, previous ipsilateral lobectomy/pneumonectomy, significant loculations likely to preclude effective fluid drainage, significant visual impairment and inability to consent or comply with the study protocol.

Randomisation and Masking: The randomization was performed independently by the National Health & Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Australia. Participants were randomized 1:1 to aggressive (daily) or symptom-guided drainage via their IPC, using an automated telephone-based voice-response randomization service. Randomization code generation was assigned sequentially as participants underwent the randomization process. Randomization was minimized for i) cancer type (mesothelioma vs non-mesothelioma), ii) performance status (Eastern Cooperative Oncology Group [ECOG] 0-1 vs ≥ 2), iii) presence of trapped lung (vs not) and iv) prior pleurodesis (vs not). Trapped lung was defined as air or fluid in the pleural space occupying $\geq 25\%$ of the lateral chest wall after initial drainage. Minimization is a dynamic method; as such there was no 'sequence'. Allocation concealment was additionally maintained by incorporating an 'imbalance window' (set at 3) within which treatments were completely random (the order of the random allocations was maintained within the NHMRC Clinical Trials Centre secure database). Participants who

withdrew from the trial were not replaced. It was not practical or possible to mask the participants or those giving the interventions.

Trial Intervention: IPC (Rocket Medical plc, UK) was inserted as per standard clinical practice. Participants were randomized within 72 hours of IPC insertion after maximum pleural fluid evacuation to ensure the same baseline for all participants. In the *Aggressive* drainage arm, participants (and/or their carers/community nurses) were asked to drain their MPE via the IPC every day for the first 60 days unless clinically contraindicated or spontaneous pleurodesis had occurred. For the *Symptom-guided* arm, participants performed drainage when they had effusion-related symptoms (usually breathlessness, cough and/or chest tightness). IPC was accessed at least fortnightly to ensure the catheter remained patent and to assess if fluid was still being produced.

Participants were supplied with standard IPC vacuum-suction bottles (600mL) for fluid drainage following instructions of the manufacturer (Rocket Medical plc, UK). Pleurodesis was defined as <50mL of fluid removed at three consecutive drainages⁶ (in the *Aggressive* drainage arm) or at two attempts two weeks apart (in the *Symptom-guided* arm), and in the absence of significant residual pleural fluid collections on imaging.

All participants and carers were given standard IPC education on the drainage method, aftercare and potential complications, and had ready access to support services (*eg* via direct phone line) for any concerns. They were free to receive other treatments including chemo-irradiation and palliative care as recommended by treating clinicians. Participants were followed up for a minimum of 6 months after randomization or until death, whichever occurred sooner. The drainage regimen after 60 days was left to the discretion of the attending clinicians.

Participants kept a logbook of their breathlessness score recorded every day for 60 days then weekly until the end of the study. The breathlessness score was measured using a validated 100mm visual analog scale (VAS), a 100mm line anchored with ‘best breathing’ at 0mm and ‘worst breathing imaginable’ at 100mm. The pain level was also measured on a 100mm VAS scale which was anchored with ‘no pain’ at 0mm and ‘worst imaginable pain’ at 100mm.⁸ The volume of pleural fluid removed at each drainage was also recorded.

Baseline clinical data, VAS scores for breathlessness^{4,5,9} and pain, and QoL (VAS and EuroQoL-5 Dimensions-5 Levels [EQ-5D-5L]¹⁰) measures were collected prior to IPC insertion and post-randomization (72 hours after IPC insertion). Participants were reviewed at 2 and 4 weeks, and thereafter monthly for 6 months. Details of any hospital admissions were recorded, including duration, adverse events and clinical management.

Outcomes: The *primary outcome* was the mean daily breathlessness score in the first 60 days post randomization. The VAS scores were measured by two independent assessors and the average of their readings recorded. Both assessors repeated their measurements separately if initial readings differed by >3mm. If discrepancies persisted, the assessors would re-score and discuss to reach a consensus.

Secondary outcomes included

- (a) rates of spontaneous pleurodesis;
- (b) self-reported global QoL measurements using two instruments, namely the EQ-5D-5L^{11,12} and a 100mm VAS at randomization (after maximal fluid drainage), at pre-determined clinic follow-up visits 2 and 4 weeks post-randomization, and thereafter monthly up to 6 months. The EQ-5D-5L score consisted of 5 domains – mobility, self-care, usual activities, discomfort/pain and anxiety/depression. Each domain was graded by the patient from 1 (‘no problems’) to 5 (‘worst’). QoL score was also measured with a 100mm line anchored with ‘best QoL’ at 0mm and ‘worst QoL’ at 100mm;
- (c) total number of episodes and duration of hospitalization for any cause (excluding elective admissions for chemotherapy). The latter was subdivided into pleural-related (or not) hospital days, as defined previously,⁴ from randomization to death or end of 6-month follow-up;
- (d) frequency of adverse (AE) and serious adverse events (SAEs). These events were then assessed by an independent reviewer for relatedness to trial intervention;
- (e) survival.

Statistical Analyses: Data were analyzed on an intention-to-treat basis and supporting analyses were carried out adjusting for minimization variables measured at randomization of mesothelioma, ECOG score, the presence of a trapped lung and prior pleurodesis, in addition to the random effect of study center, where appropriate. All data were analyzed using the R environment for statistical computing¹³ and SAS/STAT software v9.4 (Raleigh, NC, USA).

The study was planned to enroll at least 86 patients to detect a mean difference of VAS score of 14mm between the treatment arms (5% significance, 90% power) assuming a common between-group standard deviation (S.D.) of 18.9mm (based on a previous RCT of IPC⁵) and a 10% lost-to-follow up rate. The minimal clinical important difference (MCID) for the VAS score in this setting is 19mm (95% CI 14-24mm) as per Mishra et al.⁹ The lower end of the CI of 14mm was used for this power calculation.

The difference in breathlessness scores and pain scores between the two treatment arms was analyzed using a two sample *t* test on the log transformed average scores over the first 60 days of the trial. Results are back transformed and presented as geometric means and 95% confidence intervals (CIs) and compared through a ratio of the geometric means. A two sample *t* test was used to compare the difference in rates of logbook completion between the two groups.

Time to spontaneous pleurodesis was analyzed using the Fine and Gray competing risks survival model, with competing risk being death and described with the cumulative incidence curve. Time to death was analyzed using Kaplan-Meier survival curves and Cox proportional hazards models. For all time to event analyses, hazard ratios (HR) (95% CIs) comparing the two treatment arms are provided. Differences in proportions of survival and spontaneous pleurodesis between the treatment arms were compared using chi-squared tests for independence or Fisher's exact tests. All patient hospitalization data were analyzed using Mann-Whitney tests to compare the two treatment arms with supporting analyses using negative binomial regression models. The EQ-5D-5L^{11,12} scores were converted into a single index value that generates a measure of utility ranging from -0.111 to 1.000 (1.000 indicates full health) using an online tool.¹⁴ A crosswalk value set¹⁵ was used to obtain the index value, as no EQ-5D-5L value set was available specifically for the countries included in this study. Linear mixed models were used to compare EQ-5D-5L index values and log-transformed VAS (QoL) between the two treatment arms. Fixed effects of treatment, time and the treatment by time interaction and random patient and center effects were included in the model along with effects of minimization variables and, in supporting analyses, the effect of baseline index values. Differences in least squared means (95% CI) or ratios of geometric means (95% CI) are provided. When the logbook entries were incomplete, supporting sensitivity analyses were carried out using multiple imputation with chain equations of 40 imputed datasets.

This trial is registered with the Australian New Zealand Clinical Trial Registry (ANZCTR) - ACTRN12615000963527.

Role of the funding source: The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. SM and YCGL have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

RESULTS

Participants (n=87; 41 males; median age 66.8 [59.1–74.3] years) were recruited between 20th July 2015 and 26th January 2017 and randomized to the *Aggressive* (n=43) or *Symptom-guided* (n=44) drainage arms. The groups were well matched in their age, gender, proportions of primary malignancies and trapped lung, effusion size, comorbidities, baseline symptom scores and ECOG status (Table 1). The most common underlying malignancies were lung cancer (n=34), mesothelioma (n=29) and ovarian carcinoma (n=10).

Those randomized to the *Aggressive* arm performed in total 1420 drainages (median 39 [IQR 13-57] drainages per subject) up to 60 days (the intervention period), time of pleurodesis or death (whichever earliest), out of a possible 1518 drainages, confirming good compliance. Participants of the *Symptom-guided* cohort performed 535 drainages (median 11 [IQR 7-18] per subject) in the same period. At the end of the six month follow-up period, the total number of drainages performed in the subjects in the *Aggressive* and the *Symptom-guided drainage* arms were 1999 and 1035 respectively.

Primary End-Point Data were analyzed on an intention-to-treat basis (Figure 1). Five patients did not return their logbook and therefore had no breathlessness score data; they were excluded from the primary end point analysis. There was no significant difference in the compliance rates of reporting the daily breathlessness scores between the two groups (*Aggressive* arm=81.8% vs *Symptom-guided* arm=79.7%, $p=0.74$).

The primary endpoint compared the average VAS breathlessness scores of each participant over the first 60 days of study and found no significant difference between the two treatment groups (*Aggressive drainage* arm geometric mean=13.1 (95% CI 9.8-17.4) vs *Symptom-guided drainage* arm geometric mean=17.3 (95% CI 13.0-22.0), $p=0.18$; ratio of geometric means 1.32, 95% CI 0.88-1.97), Figure 2. This was further supported in analyses adjusting for minimization variables and including random center effects (*Aggressive drainage* arm geometric mean=16.3 (95% CI 11.3-23.7) vs *Symptom-guided drainage* arm geometric mean=21.0 (95% CI 14.8-29.7), $p=0.21$; ratio of geometric means 1.28, 95% CI 0.86-1.91) and was consistent when multiple imputation was carried out to account for missing logbook entries.

Secondary End-points

Spontaneous pleurodesis Significantly more patients in the *Aggressive* arm developed spontaneous pleurodesis (n=16, 37.2%) than in the *Symptom-guided* arm (n=5, 11.4%) in the first 60 days, $p=0.0049$, and by 6 months [n=19 (44.2%) vs n=7 (15.9%) respectively, $p=0.004$]. From the competing risk survival model the HR comparing *Aggressive* to *Symptom-guided* groups for achieving spontaneous pleurodesis was 3.287 (95% CI 1.396-7.740, $p=0.0065$), Figure 3. These results were consistent after adjusting for minimization variables (HR=3.429, 95% CI 1.413-8.320, $p=0.0064$).

We compared patients with non-trapped (n=59) and trapped lungs (n=28) in a post-hoc analysis. Spontaneous pleurodesis was more common in those with non-trapped lungs than in those with trapped lungs (n=17 vs 4, 28.8% vs 14.3% respectively) at 60 days but not by 6 months (n=18 vs 8; 30.5% vs 28.6% respectively). In the *Aggressive drainage* arm, spontaneous pleurodesis developed in 41.4% of those with non-trapped lungs (vs 28.6% in the trapped lung group) at 60 days and 41.4% (vs 50.0%) at 6 months. In the *Symptom-guided* arm, spontaneous pleurodesis developed in 16.7% of those with non-trapped lungs (vs 0.0% in those with trapped lungs) at 60 days and 20.0% (vs 7.1%) at 6 months. The Kaplan-Meier estimated median time to pleurodesis was 121 days in the *Aggressive* arm, including those with trapped and non-trapped lungs. The success rate was too low in the *Symptom-guided* arm to provide a reliable Kaplan-Meier estimate of the median time to pleurodesis.

Pain scores The mean (SD) of the VAS pain scores over the first 60 days of the trial was 10.74 (12.80) in the *Aggressive* arm and 16.31 (16.58) in the *Symptom-guided* arm (Figure 4), and there was no significant difference between the treatment (ratio of geometric means=1.28, 95% CI 0.76-2.18, $p=0.35$).

QoL Scores In a linear mixed model on response to EQ-5D-5L, no interaction between time and treatment was detected and the significant main effect of treatment arm indicated that the averaged EQ-5D-5L index values over the study period/visits were higher (i.e. better QoL) in the *Aggressive* arm than in the *Symptom-guided* arm: estimated means 0.713 (95% CI 0.647-0.779) vs 0.601 (95% CI 0.536-0.667) respectively. The estimated difference in means was 0.112 (95% CI 0.0198-0.204), $p=0.0174$. This was consistent after adjusting for minimization variables and baseline EQ-5D-5L index values (estimated difference in

means=0.097, 95% CI 0.004-0.191, $p=0.0408$). No between-group differences were found in the VAS (QoL) scores during the study visits (ratio of geometric means=1.220, 95% CI 0.871-1.709, $p=0.25$). For all visit times for both treatments there was concordance in the measures of EQ-5D-5L and the VAS QoL with statistically significant correlations at most of the visit times and moderate to high correlations throughout (see Online Supplementary).

Hospital admissions and total number of days in hospital The median number of hospital admissions was 1 [IQR 0-2] for the first 60 days and 2 [1-3] at 6 months for the entire cohort. Overall, the trial patients spent 1 [IQR 0-8] day in total in hospital by 60 days and 5 [0-15] days by 6 months. There were no differences between the *Aggressive drainage* and the *Symptom-guided drainage* arms in the number of hospital admissions or duration spent in hospital either in total number of days or when only the effusion-related admissions were included (as defined in our previous trial⁴), Table 2. These results were consistent after adjusting for days in trial and other minimization variables.

Patients with better (ECOG 0-1) performance status spent fewer effusion-related days in hospital at 60 days (1 [IQR 0-2] vs 2 [0-6] days, $p=0.0392$) and by 6 months (1 [IQR 0-4] vs 2 [0-6] days, $p=0.0339$) than those of ECOG ≥ 2 . Trapped lung at baseline was associated with fewer episodes of hospital admissions (1 [IQR 0-2] vs 2 [1-3] without trapped lung, $p=0.0406$), total (2.5 [IQR 0-6] vs 6 [1-19] days, $p=0.0013$) and effusion-related days in hospital (1 [IQR 0-3] vs 1 [0-6] day, $p=0.0158$) at 6 months.

Mortality No significant differences were observed between the treatments for time to death at 6 months (*Aggressive vs Symptom-guided drainage* arms HR 0.951; 95% CI 0.499-1.812, $p=0.88$), see Kaplan-Meier analyses (Figure 5). In the first 60 days, 10 (23.3%) individuals in the *Aggressive drainage* arm and 9 (20.5%) in the *Symptom-guided drainage* arm died (estimated difference in proportions=0.028, 95% CI -0.146-0.202, $p=0.75$). By 6 months, 18 (41.9%) patients in the *Aggressive drainage* arm and 19 (43.2%) in the *Symptom-guided drainage* arm had died (estimated difference in proportions=-0.013, 95% CI -0.221-0.195, $p=0.90$).

Patients with better performance status by ECOG score also had longer survival (HR for death for better to poorer ECOG status=0.399, 95% CI 0.203-0.785, $p=0.0078$) at 6 months.

Adverse events The total number and proportion of patients experiencing ≥ 1 AE or SAE are presented (Table 3). Of the 32 SAEs and 46 AEs recorded, 11 (four SAEs, and seven AEs) were deemed definitely not related to trial intervention by an independent assessor. Eleven patients in the *Aggressive drainage* arm and 12 in the *Symptom-guided drainage* arm had experienced SAEs. AEs (n=46) occurred in 13 and 22 patients in the *Aggressive drainage* and *Symptom-guided drainage* arms respectively. In the *Symptom-guided* arm, the most common adverse event was pain at IPC site pain requiring narcotics (n=12). Worsening dyspnea due to ipsilateral pleural effusion despite drainage occurred in six patients which usually responded well to increasing drainage frequency.

Eleven episodes of pleural infection developed (n=5 vs 6 in the *Aggressive drainage* and *Symptom-guided drainage* arms respectively) in 9 patients over 6 months. Four patients had their IPC removed at the time of infection and three others developed pleurodesis post-infection. There were no deaths related to IPC infection.

DISCUSSION

This multicenter RCT found no differences between the aggressive (daily) and the symptom-guided drainage approaches in providing breathlessness control over the first 60 days post-IPC insertion. There were no significant between-group differences in pain, days spent in hospital or survival. *Aggressive* drainage was associated with a higher rate of pleurodesis and better EQ-5D-5L index values. Serious adverse events were uncommon in either group.

MPEs are common and affect about one-third of those with lung and breast cancers and the majority of mesothelioma patients. MPE often heralds incurable cancers and limited prognosis.¹⁶ Control of the associated breathlessness frequently requires invasive pleural procedures. IPC presents an alternative to conventional talc pleurodesis, and has been shown to reduce hospitalization^{4,5,17} and need for repeat pleural interventions in the patients' remaining lifespan.^{4,5} The use of IPC is growing rapidly, especially in developed countries, and is often advocated as the first-line definitive therapy for MPE.¹⁸ Ambulatory IPC drainages do require resources (time of carers/community nurses and consumables) and theoretically can introduce infections.¹⁹ Two schools of IPC management, *aggressive* and *symptom-guided* drainage approaches, have evolved and are at equipoise.

Our study found no significant differences in breathlessness control, the principal goal of MPE palliation, whether the patients perform drainages daily or as guided by symptoms. The data are reassuring and imply that if assigned to do so, patients were able to recognize early, or anticipate, their symptoms and perform drainages before any discomfort reached a level of impact.

However, aggressive daily fluid removal did promote more effective pleurodesis. Keeping the pleural cavity fluid-free theoretically allows better approximation of the visceral and parietal pleura and thus adhesion formation and pleural fibrosis/symphysis. Conversely, permitting 'asymptomatic' accumulation of the pleural fluid in between symptom-guided drainages may have physically impaired pleural symphysis. A prior RCT also found that spontaneous pleurodesis occurred more commonly with daily than alternate day drainages.⁶

Most spontaneous pleurodesis in the *Aggressive drainage* arm developed within the first 60 days, consistent with timeframe from published data.^{6,20} In our protocol, the drainage schedules

after 60 days were left to the choice of the attending clinicians and patients. It is possible that without the suggestion of slowing down of drainage, many patients would have adopted a less aggressive approach. Whether prolonging daily drainage beyond 60 days will facilitate late pleurodesis requires further research.

Our study is one of the very few RCTs that included patients with trapped lung, which accounted for a third of the cohort, consistent with commonly quoted data. Those with trapped lung had (expectedly) a lower rate of pleurodesis than those with expandable lung, though aggressive drainage was still associated with a higher pleurodesis rate even in the trapped lung group. The exact mechanism will need exploration although it is possible that in some cases the trapped lung can slowly expand with time (and/or concurrent therapy) and allow pleural symphysis. Alternatively, the trapped space may be small and when sufficient adhesions/loculations develop over time, no further fluid drainage is necessary. Nonetheless, future studies should incorporate trapped lung patients to guide best care.

Reassuringly, aggressive drainage was not associated with more pain or infection. IPC-related pleural infection affected about 5% of patients in our previous international study.²¹ Daily access of the catheter may increase risks of introducing microbes; however, pleural drainage is the key to empyema management and aggressive drainage may ensure prompt removal of any microbes that have entered the pleural cavity. There were also no major differences in other serious adverse events or survival between the two arms. More AEs were observed in the *Symptom-guided* drainage arm especially dyspnea attributed to pleural effusion, most of which responded to increased frequency of drainage.

Patients in the *Aggressive* drainage arm reported better EQ-5D-5L index values, despite no clear benefits in their reported breathlessness or pain scores. There is no MCID specifically assigned for patients with MPE for EQ-5D-5L or VAS-QoL. In our study, the between-group difference of the EQ-5D-5L index value was 0.112 which is above the MCID defined by Pickard et al²² (=0.09) in advanced cancer patients. It is possible that daily removal of the fluid provided benefits in symptoms not captured with our breathlessness and pain measurements. The higher pleurodesis rate, with resultant freedom from fluid (and symptom) recurrence and of the catheter, may have contributed to the better reported QoL. Additionally, it has been suggested that IPC drainage gives patients an important sense of control when they are feeling helpless with their advancing cancer. Whether this can explain the scores remains to be tested.

The two QoL instruments both showed improvements and there exists good correlations of the values between the EQ-5D-5L and VAS-QoL at each time point. The between-group differences were significant with EQ-5D-5L but not with VAS-QoL. This may be related to the sensitivity of the instruments in detecting changes in this patient population, but this is a topic for future studies.

Developing the full potential of IPC in MPE care is a topic of active research. Combining IPC with pleurodesis, either by instillation²⁰ via the catheter or coating²³ of the catheter with a pleurodesing agent, appears promising. Defining the best drainage regimen will hold an even more important role if instillation of pleurodesing agents becomes routine practice. A newly published randomized trial²⁰ showed that instillation of talc slurry (followed by IPC drainage 2-3 times a week) induced a higher rate of pleurodesis than saline control. However, the success rate in the talc arm was low (~43%), similar to what was achieved with our *Aggressive drainage* arm (without talc). Our trial, and the ASAP study,⁶ both confirmed that daily IPC fluid removal enhances spontaneous pleurodesis, which is adopted now into protocols of ongoing studies (*eg* EPIToME and OPTIMUM²⁴) evaluating talc instillation via IPC.

Our study has limitations. First, the primary endpoint was set at 60 days as it reflects the short median survival of MPE from lung cancers (the most common type of MPE globally). We have however also included many MPEs from mesothelioma (the subtype with longest median survival among common causes of MPEs). Our results did not differ between the non-mesothelioma and mesothelioma patients. Second, the definition of ‘spontaneous pleurodesis’ used in existing literature describes cessation of fluid formation, which may relate to treatment or natural disease course, but not necessarily symphysis of the visceral and parietal pleura (the true meaning of ‘pleurodesis’). Ultrasound assessment was available in a subset of 18 patients who had ‘spontaneous pleurodesis’ in the lead center; all but one achieved sonographic appearances of pleural symphysis. Third, the consumable/carer costs of daily drainage varied substantially among centers around the world. However, this study has provided an idea of the amount of drainage consumables needed for aggressive and symptom-guided drainage and would allow clinicians to estimate their local costs of each regimen. Fourth, as our study is an open label study, there can be potential of introducing bias with the use of patient reported measures.

Recently published and ongoing RCTs in MPE management have provided data supporting the use of IPC as first choice definitive management in MPE,^{4,5,25,26} but realizing its full potential depends on employing the optimal drainage schedule. This present trial showed that either *aggressive* or *symptom-guided drainage* regimens are adequate in breathlessness control. However, daily fluid removal enhances spontaneous pleurodesis and may improve QoL without any drawbacks in relation to pain, infection rates or survival. In patients where pleurodesis is an important goal, e.g. those undertaking strategies of IPC plus pleurodesing agents, aggressive drainage should be employed for at least 60 days. Future studies will need to establish if more aggressive, e.g. twice daily, regimens for the initial phase may further enhance success rates.²⁷ On the other hand, for patients whose primary care aim is palliation, e.g. those with very limited life expectancy or significant trapped lung where pleurodesis is unlikely, our data showed that symptom-guided drainage offers an effective means of breathlessness control without the inconvenience and costs of daily drainages. The ability to predict likelihood of pleurodesis will help guide choice of regimen and should be a topic of future studies.

Contributors

SM and MA are joint first authors. Guarantor – YCGL; SM and YCGL have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Trial conception, design, and protocol - YCGL, SM, MA, RT, NAM, DF-K, KM; Patient recruitment and data collection – DBF, RS, BCHK, DCLL, CCdeC, MRSRA, EY, CLT, LAG, PTN, CS, NDP; Statistical Analyses – KM, CAB; Trial and database management – CAR; Independent review of hospital discharge and adverse events data - CK; Manuscript writing and final approval - all authors.

Declaration of Interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Rocket Medical plc (UK) provided the drainage kits for the study participants without charge. YCGL, DFK and NAM have served on the advisory board of CareFusion/BD Ltd. NAM has received an unrestricted educational grant from Rocket Medical

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LEGENDS

Figure 1: Trial profile

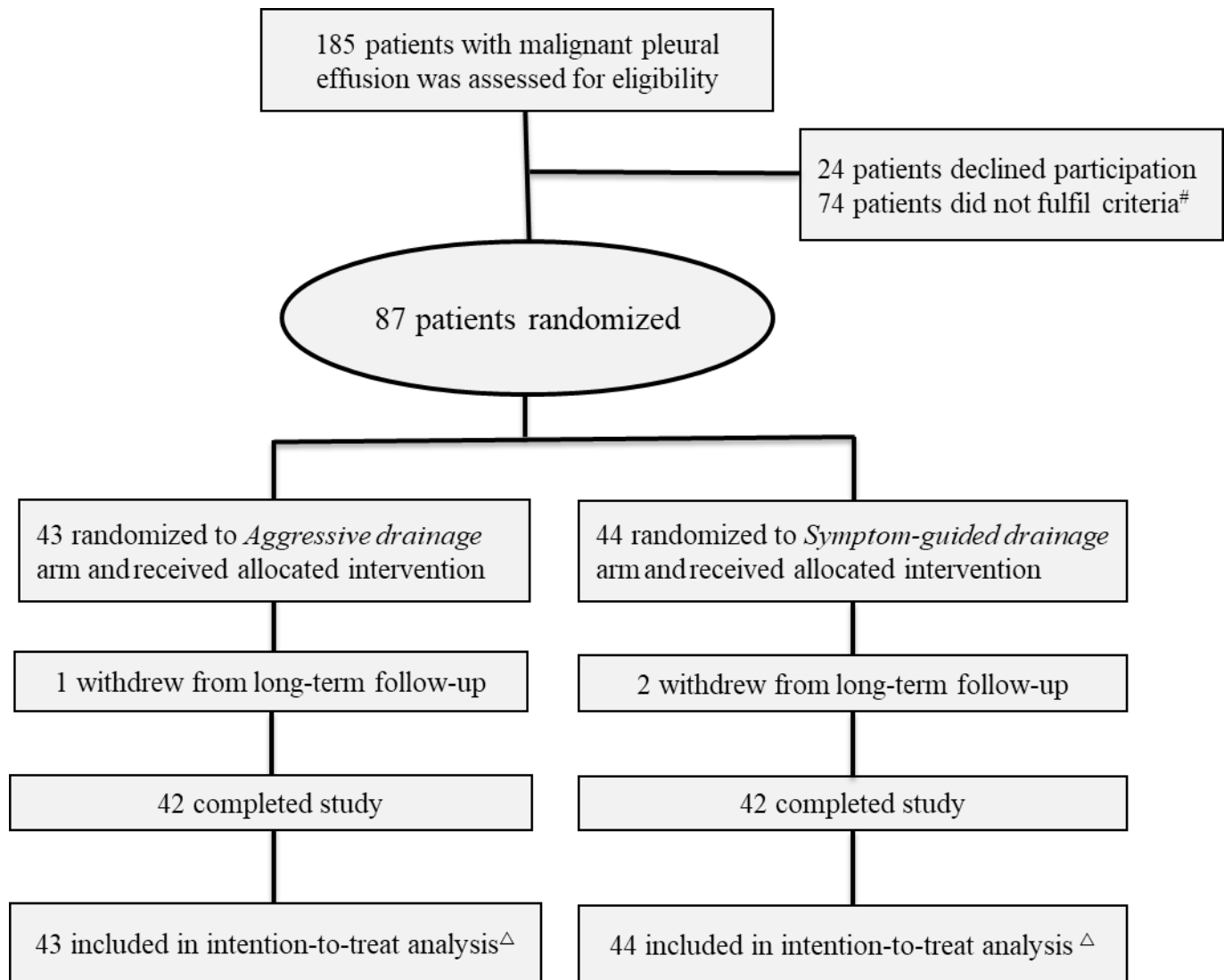
Figure 2. The average VAS breathlessness scores of each individual patient over the first 60 days by treatment group are presented. The minimal clinically important difference of this instrument is 19mm for malignant pleural effusion patients. The horizontal lines indicate the median values.

Figure 3. Cumulative incidence curve of pleurodesis success rate based on 6 months data estimated from Fine and Gray competing risks model. Note: Three individuals withdrew from the study during the 6 month follow-up: one from the *Aggressive* arm at 173 days and two from the *Symptom-guided* arm at 52 and 97 days.

Figure 4. The average VAS pain scores of each individual patient over the first 60 days of the trial are presented. The horizontal lines indicate the median values.

Figure 5. Kaplan-Meier curve of survival at 6 months

Figure 1: Trial profile



74 patients were screened but found ineligible for the following reasons: Expected survival < 3 months (n=27); unable to comply with protocol (n=12); effusion did not have histo-cytological confirmation as malignant (n=7); effusion not causing symptoms (n=4); critical illness (n=3); significant loculations (n=3); chylothorax (n=2); uncorrectable bleeding diathesis (n=2); inability to consent (n=2); previous ipsilateral IPC (n=2); visual impairment (n=1); concurrent pleural infection (n=1); previous ipsilateral lobectomy (n=1); not specified (n=7).

^ 5 patients (2 in *Aggressive* and 3 in *Symptom-guided* arm) did not return any logbook data for primary endpoint analysis.

Figure 2. The average VAS breathlessness scores of each individual patient over the first 60 days by treatment group are presented. The minimal clinically important difference of this instrument is 19mm for malignant pleural effusion patients. The horizontal lines indicate the median values.

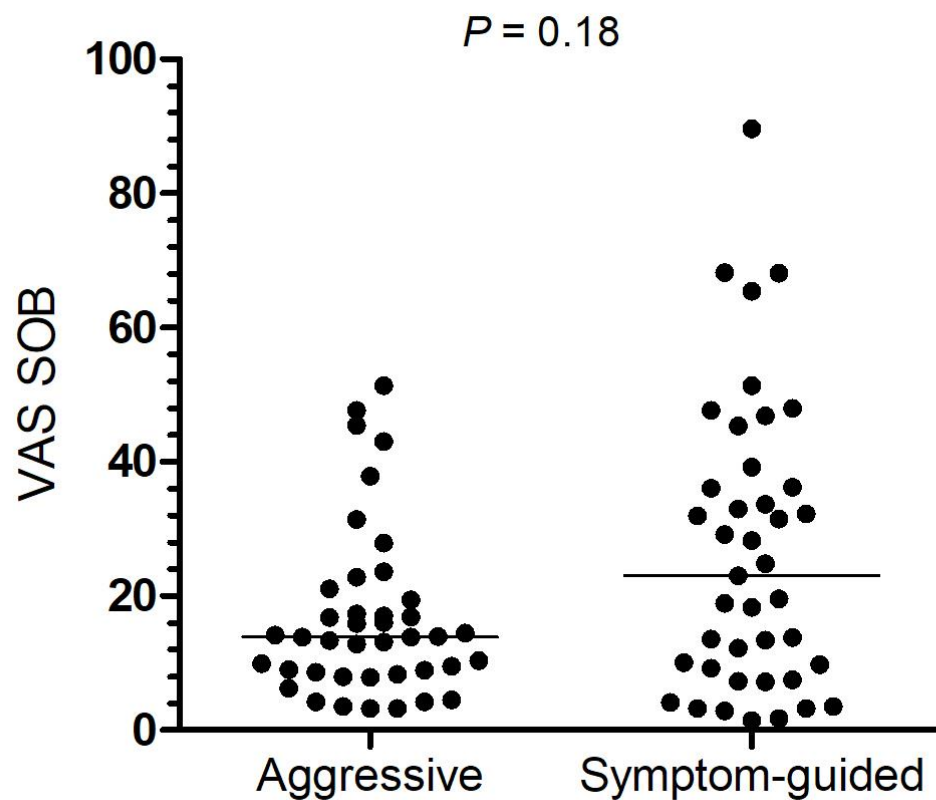
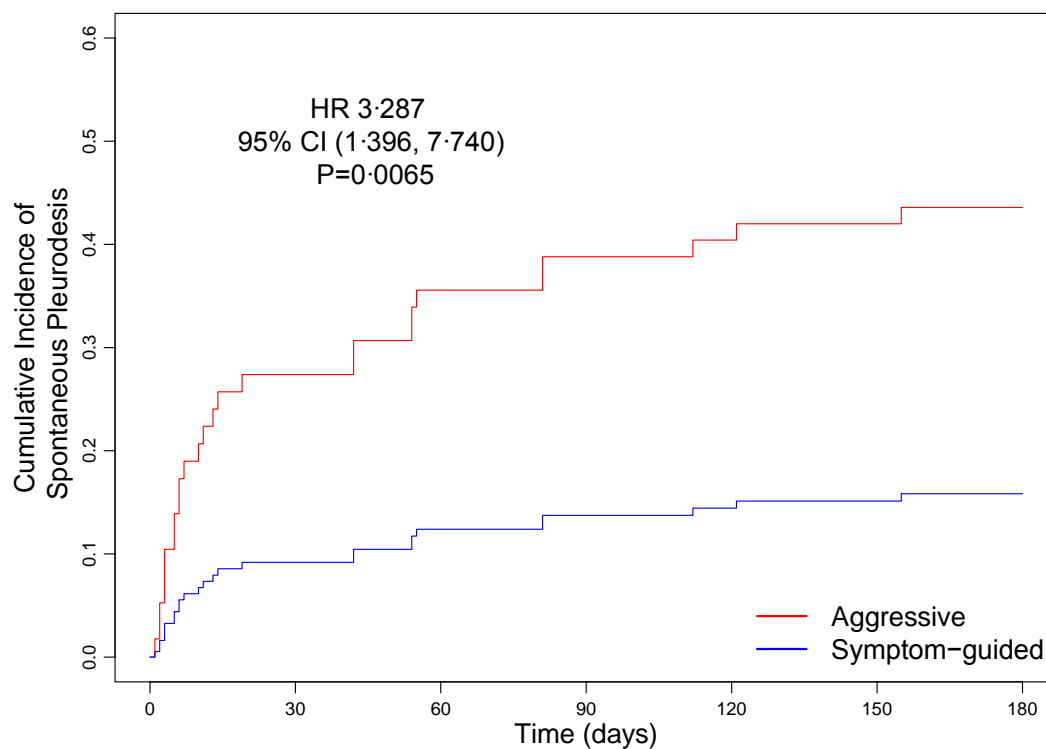


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	Number at risk						
Aggressive	43	27	17	13	11	10	7
Symptom-guided	44	33	29	28	23	19	17

Figure 4. The average VAS pain scores of each individual patient over the first 60 days of the trial are presented. The horizontal lines indicate the median values.

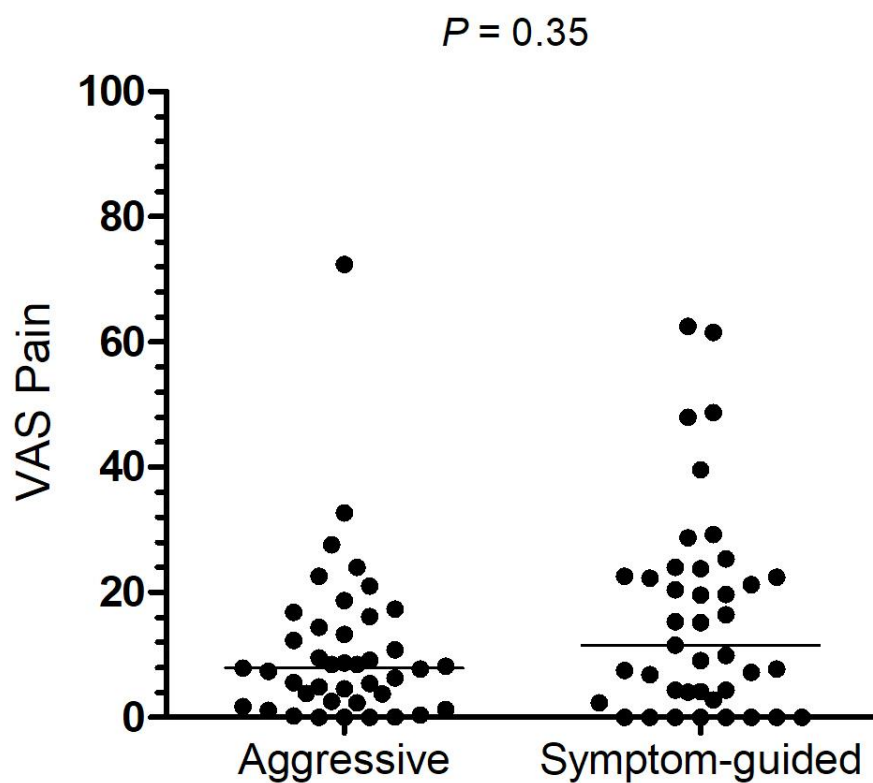
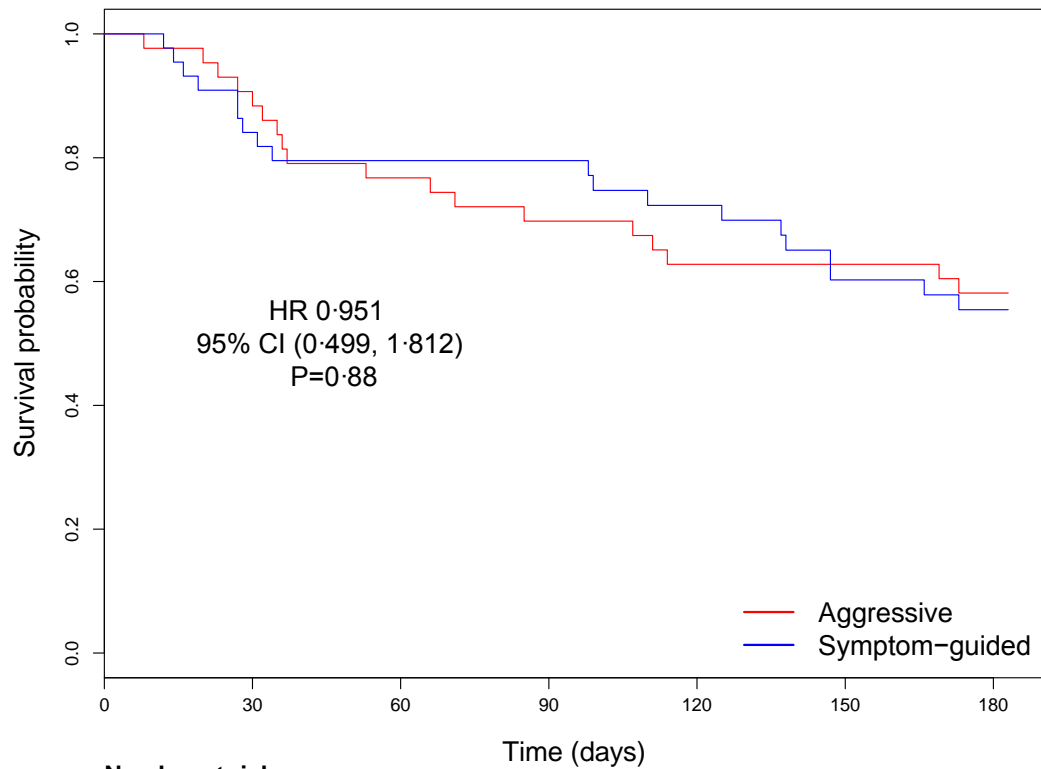


Figure 5. Kaplan-Meier curve of survival at 6 months



	Number at risk						
	0	30	60	90	120	150	180
Aggressive	43	39	33	30	27	27	24
Symptom-guided	44	37	34	34	30	25	23

Table 1. Summary statistics of baseline measures are provided by treatment arm including counts and percentages for categorical variables.

	<i>Aggressive drainage</i> (n=43)	<i>Symptom-guided drainage</i> (n=44)
Age (median [IQR] years)	65.1 [57.8-72.5]	68.0 [60.8-75.0]
Male gender n= (%)	21 (49%)	20 (45%)
Side of intervention: right n= (%)	27 (63%)	31 (71%)
Type of primary malignancy n= (%)		
Mesothelioma	15 (35%)	14 (32%)
Non-mesothelioma	28 (65%)	30 (68%)
Lung	17 (40%)	17 (39%)
Breast	0 (0%)	4 (9%)
Ovarian	6 (14%)	4 (9%)
Other	5 (12%)	5 (11%)
Trapped lung n= (%)	14 (33%)	14 (32%)
Previous Talc Pleurodesis n= (%)	4 (9%)	7 (16%)
ECOG Performance Status		
0 – 1	30 (70%)	30 (68%)
≥2	13 (30%)	14 (32%)
Comorbidities n= (%)		
Respiratory	8 (19%)	13 (30%)
Cardiac	9 (21%)	8 (18%)
Depression/Anxiety	9 (21%)	6 (14%)
Diabetes	6 (14%)	6 (14%)
Effusion size grade # n= (%)		
Small (0 – 1)	1 (2%)	1 (2%)
Moderate (2 – 3)	13 (30%)	14 (32%)
Large (4 – 5)	29 (67%)	29 (66%)
Baseline self-reported symptom scores mean (SD)		
VAS breathlessness score (mm)	28.1 (20.3)	28.3 (20.7)
VAS QoL score (mm)	36.4 (22.4)	29.8 (19.9)
EQ-5D-5L index score	0.681 (0.177)	0.611 (0.231)
EQ-5D-5L Score by modality median [IQR]		
Mobility	1 [1-2]	2 [1-3]
Self-care	1 [1-2]	1 [1-2]
Usual activities	2 [2-3]	2 [1-3]
Pain/Discomfort	2 [2-3]	2 [2-3]

Depression/Anxiety	1 [1-2]	2 [1-2]
Chemotherapy in preceding 30 days n= (%)	9 (21%)	11 (25%)

ECOG=Eastern Cooperative Oncology Group. VAS=Visual Analog Scale. QoL= quality-of-life. IQR=interquartile range. EQ-5D-5L = EuroQoL-5 Dimensions-5 levels.

Baseline effusion size was graded on chest radiograph using a validated grading system whereby grade 0 referred to no radiographic evidence of pleural fluid; grade 1 = blunting of the costophrenic angle; grade 2 to 5 referred to fluid occupying <25%, 25 to 50%, 51 to 75% and >75% of the hemithorax respectively.²⁰ This scale has previously been used to predict pleurodesis and indwelling pleural catheter use in patients with a malignant pleural effusion.²¹

Table 2. Data of hospital admissions in episodes and duration by treatment groups. All values presented as median [IQR].

	Aggressive Drainage (n=43)	Symptom- guided Drainage (n=44)	<i>p</i> =
Episodes of hospital admission			
<i>First 60 days</i>	1 [0-2]	1 [0-2]	0.74
<i>At 6 months</i>	2 [1-4]	2 [1-3]	0.80
Total days spent in hospital			
<i>First 60 days</i>	1 [0-7]	1.5 [0-8]	0.84
<i>At 6 months</i>	5 [0-15]	4 [1-15.5]	0.52
Effusion-related hospitalization days			
<i>First 60 days</i>	1 [0-4]	1 [0-3]	0.74
<i>At 6 months</i>	1 [0-5]	1 [0-5]	0.70

Table 3. Adverse and Serious Adverse Events by treatment groups.

Type of Events	Aggressive Drainage (n=43)	Symptom-guided Drainage (n=44)
Total Serious Adverse Events (SAE) n=	16	16
Total Adverse Events (AE) n=	14	32
TOTAL AEs and SAEs	30	48
Number of patients affected by a SAE n=	11	12
Number of patients affected by an AE n=	13	22

<i>Events assessed to be ‘Definitely’, ‘Probably’, ‘Possibly’, or ‘Unlikely’ related to trial intervention by an independent assessor</i>		
Serious Adverse Events n=		
Pleural Infection	5	6
Symptomatic loculation	3	5
Air leak/Pneumothorax	2	1
Recurrence needing re-intervention post IPC removal	1	1
IPC site cellulitis requiring hospital admission	2	0
IPC blockage requiring hospital admission	0	1
Worsening dyspnea (effusion related) requiring hospital admission	0	1
Adverse Events n=		
IPC blockage	1	3
IPC site cellulitis	1	2
Pain requiring narcotics		
IPC site	7	12
Related to suction bottle	1	1
IPC leakage	0	1
IPC valve dislodged	0	1
Worsening dyspnea		
Effusion related	1	6
Recurrence needing re-intervention	0	1
Not effusion related	0	1
<i>Events assessed to be ‘definitely not related’ to trial intervention</i>		
	6	5