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RESEARCH LETTER

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Inoperable chronic thromboembolic pulmonary hypertension: Evolution of prognosis over 10 years of new emerging therapies

Abstract

Therapies for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) include balloon pulmonary angioplasty (BPA) and PH-specific medical therapy. This study compares survival and its predictors before and after the introduction of BPA. BPA was independently associated with survival; however, there was no difference in overall survival between the two cohorts.

KEYWORDS

chronic thromboembolic pulmonary hypertension, prognosis, pulmonary embolism, pulmonary hypertension, survival

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of pulmonary embolism.[1] The treatment of choice for all eligible CTEPH patients is pulmonary endarterectomy (PEA).[2] Riociguat, the only US Food and Drug Administration (FDA)-approved pulmonary hypertension (PH)-targeted medical therapy, is recommended for the treatment of inoperable CTEPH.[3,4] In addition, other PH-targeted medical therapies, such as endothelin receptor antagonists (ERA) or phosphodiesterase inhibitors (PDE5i), may be considered.[3] Currently, the majority of inoperable CTEPH patients in the Netherlands are treated with dual PH-targeted therapy.[5] A second treatment option in inoperable CTEPH is balloon pulmonary angioplasty (BPA).[6,7] This percutaneous treatment is safe and effective by improving hemodynamics, exercise capacity, and quality-of-life.[7,8]

There are limited studies reporting survival rates in inoperable CTEPH. Three-year survival rate ranges between 70% and 75% and the positive effect of BPA on survival is suggested.[9–11] In addition to treatment strategies, cardiovascular comorbidities may influence mortality in PH patients.[12]

Therefore, the main objective of this study was to report long-term survival of inoperable CTEPH patients and to analyze two cohorts: before (2010–2014) and after the introduction of BPA (2015–2019). Furthermore, we try to evaluate the prognostic role of treatment strategies and cardiovascular comorbidities on survival.

METHODS

Patient selection

For this study, all consecutive inoperable CTEPH patients diagnosed between 2010 and 2019 were included from two PH expertise centers (Erasmus MC and St. Antonius Hospital) in the Netherlands.

CTEPH was defined according to the ESC/ERS guidelines at the time.[13] Diagnosis and operability were assessed by a multidisciplinary CTEPH team.[3,13] The date of baseline right heart catheterization was used as date of diagnosis. Patients were categorized based on that date in

two cohorts: before (2010–2014) and after the introduction of BPA (2015–2019).

Data collection

Available baseline parameters were retrieved from electronic patient records. Treatment with PH-targeted medical therapy was evaluated at 1-year follow-up. Cardiovascular comorbidities were defined according to the criteria outlined in the GRIPHON study.[12] The endpoint, all-cause mortality, was evaluated by consulting government death registries on December 31, 2022. The patients diagnosed between 2010 and 2014 who were reassessed and underwent BPA were censored on the date of the first BPA, to minimalize immortal time bias. Patients who did not reach the endpoint were censored on December 31, 2022.

Statistical analysis

Categorical data and continuous variables were analyzed and reported appropriately. Survival analysis was performed using Kaplan–Meier survival analysis stratified by time cohort. The log-rank test was used for comparison between the time cohorts.

Multiple imputations via chained equations were used to create 20 imputed data sets with 20 iterations for missing values. A multivariable Cox proportional hazards model was used to assess the association between cardiovascular comorbidities or treatment and survival. Variables for the multivariable analyses were selected by both backward selection (cut-off $p < 0.15$) and clinical relevance. The study protocol was approved by the medical ethics committee of both participating centers (MEC-U, Z18.039).

RESULTS

Study population

For this study, 258 CTEPH patients were screened between 2010 and 2019, of which 74 patients were excluded due to previous PEA. One hundred eighty-four patients were included in this study (mean age 66.7 ± 13.3 years, 58.2% female, 54.9% New York Heart Association Functional Classification III/IV). Both cohorts, 2010–2014 and 2015–2019, included 92 patients. The recent cohort consisted of less females (50.0% vs. 66.3%; p value: 0.04) and tended to be older (68.4 ± 12.0 vs. 65.0 ± 14.3 years; p value: 0.09), with a lower body mass index (BMI) (26.8 ± 5.4 vs. $28.4 \pm 5.9\ kg/m^2$; p value: 0.06). The PAWP was lower in the recent cohort (10 [6–13] vs. 12 [10–14] mmHg; p value: 0.002). Data are summarized in Table S1.

Therapy strategies

Riociguat (9.3% vs. 37.9%; p value: <0.001) was used more often in the recent cohort. Likewise, in the recent cohort, more patients received dual PH-targeted therapy (p value: 0.004) at 1-year follow-up. Data at 1-year follow-up were not available in nine patients (eight died within first year and missing data in one). Sixteen patients (17.4%) of the old cohort received BPA after 2015. Two patients were treated with prostacyclin analogs, one in each cohort, see Table S1.

Survival

Sixty-two patients (34%) died during a median follow-up time of 5.8 years (interquartile range: 3.8–8.8 years). The overall 1-, 3-, and 5-year survival was respectively: 96%, 84%, and 74%. There was no significant difference in survival observed between the recent and old cohort (p value: 0.37), shown in Figure 1.

Multivariate cox regression analyses showed that higher right atrium pressure (RAP; hazard ratio [HR]: 1.08 [95% confidence interval [CI]: 1.02–1.15]; p value: 0.01) and higher NT-proBNP (HR 1.54 [95% CI: 1.20–1.97] per log unit; p value: 0.001) at baseline were associated with higher all-cause mortality, while BPA treatment (HR 0.22 [95% CI: 0.08–0.56]; p value: 0.002) was associated with lower all-cause mortality. A medical history of systemic hypertension increased the risk of death (HR: 1.76 [95% CI: 1.02–3.05]; p value: 0.04). Both pulmonary vascular resistance and BMI $\geq 30\ kg/m^2$ at baseline were not associated with all-cause mortality (Figure S1).

DISCUSSION

We reported an overall 1-, 3-, and 5-year survival of inoperable CTEPH patients of respectively 96%, 84%, and 74%. In the recent cohort, more patients were treated with BPA and dual PH-specific therapy. BPA treatment was associated with an increased survival, while systemic hypertension and higher RAP were associated with worse survival.

The 1-, 3-, and 5-year survival rates observed in our study seem to be higher compared to those

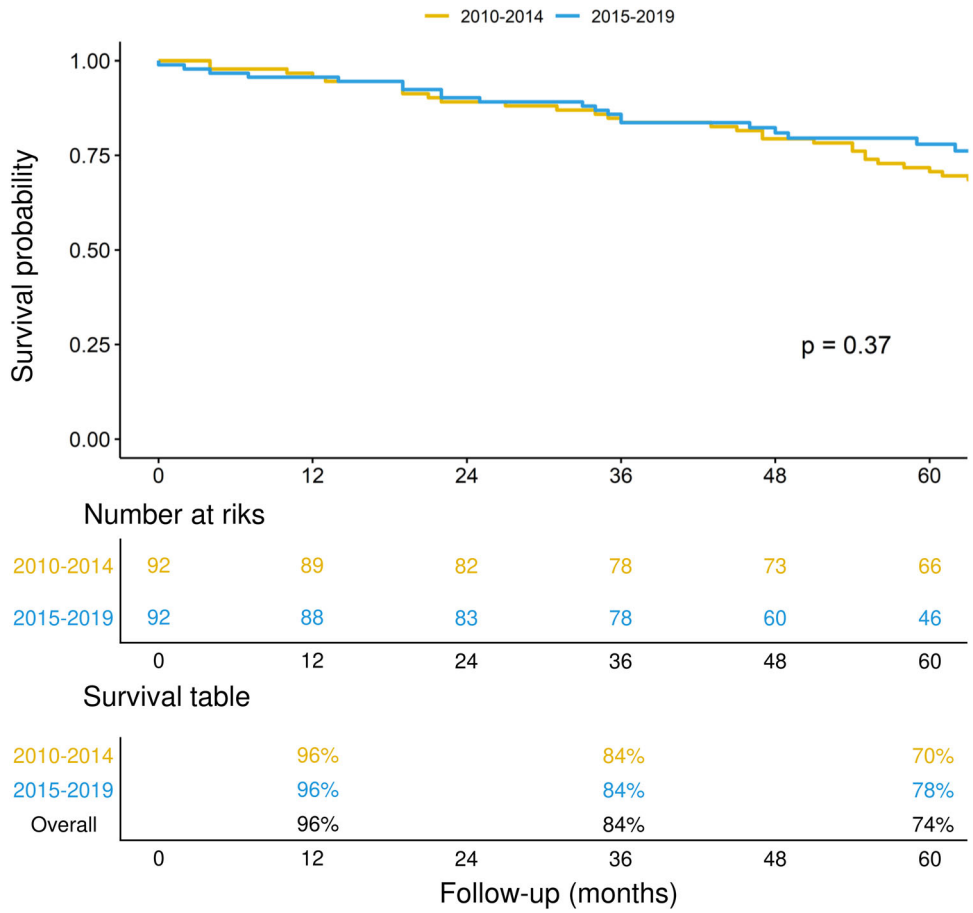

FIGURE 1 Kaplan–Meier curve of the old and recent cohort of inoperable chronic thromboembolic pulmonary hypertension patients.

reported in France (respectively, 90%, 78%, 64%).[9] While baseline characteristics were comparable between both studies, pulmonary hemodynamics were more favorable in our study. This may partially explain our better survival outcomes. An international prospective registry published in 2016 also showed lower survival rates at 1- and 3-year follow-ups: 88% and 70%, respectively.[10]

In the recent cohort, the patients diagnosed with inoperable CTEPH tended to be older. A small study in Latvia reported similar results, where the age of CTEPH patients at first diagnosis increased between 2007 and 2017.[14] Increase in age is associated with a higher risk of all-cause mortality.[15] Despite the older age in the more recent group, the survival rates were similar. This might be due to the improvement in quality of care, including the introduction of new therapies.

Even though no difference in survival between the two time cohorts was observed, the multivariable analyses showed that BPA was independently associated with improved survival. This is in line with previous findings.[16] Furthermore, our results confirmed that a lower RAP and NT-proBNP at baseline are predictors of better survival.[9]

In accordance with the method of the GRIPHON post hoc analyses, we analyzed the association between cardiovascular comorbidities and survival[12] and that systemic hypertension is associated with worse survival. Whereas the GRIPHON post hoc analyses reported no influence of comorbidities on morbidity or mortality in pulmonary arterial hypertension patients treated with selexipag.[12]

In terms of PH-targeted therapy treatment strategies, our results showed an increase in the use of riociguat with concomitant decrease in the use of PDE5i. These numbers were expected since both riociguat and PDE5i act on the same cyclic guanosine monophosphate pathway and riociguat became FDA-approved for CTEPH in 2013.[3,4] Furthermore, in the recent cohort more patients were treated with dual combination therapy. This reflects the results of the MERIT-1 trial, which showed a significant improvement of PVR in inoperable CTEPH patient randomized to macitentan, while 60% of the included patients were already on PH-targeted therapies.[17]

LIMITATIONS

The classification into two cohorts was based on the introduction of BPA in our country. We therefore censored first cohort patients who underwent BPA on the date of their first BPA. As previously mentioned, BPA treatment is a predictor of improved survival. The association with all-cause mortality may be susceptible to confounding by indication, attributable to the selective patient enrollment for BPA procedures. Furthermore, introduction of new PH-targeted medication and combination therapy may have also influenced our results. Therefore, it is difficult to draw conclusions about the association between the use of different PH-targeted therapies and survival.

Because this study was conducted in only two Dutch PH expert centers, it incorporates a relatively small number of patients, potentially limiting statistical power. Another important limitation is residual confounding, which could be attributed to the observational study design.

CONCLUSION

The 1-, 3-, and 5-year survival of inoperable CTEPH patients was 96%, 84%, and 74%, respectively. Systemic hypertension, higher NT-pro BNP levels, and RAP were associated with worse survival. Treatment with BPA for eligible patients was associated with a significantly better survival.

AUTHOR CONTRIBUTIONS

Conceptualization: Diederik P. Staal, Paul M. Hendriks, Liza D. van de Groep, Annemien E. van den Bosch, Karin A. Boomars, and Martijn C. Post. *Patient inclusion*: Leon M. van den Toorn, Berend-Jan M. Mulder, Prewesh P. Chandoesing, Robert M. Kauling, Sanne Boerman, Annemien E. van den Bosch, Hans-Jurgen Mager, Karin A. Boomars, and Martijn C. Post. *Data curation*: Diederik P. Staal and Paul M. Hendriks. *Data analysis*: Diederik P. Staal and Paul M. Hendriks. *Supervision*: Mitch C. J. van Thor, Leon M. van den Toorn, Berend-Jan M. Mulder, Prewesh P. Chandoesing, Robert M. Kauling, Sanne Boerman, Annemien E. van den Bosch, Hans-Jurgen Mager, Karin A. Boomars, and Martijn C. Post. *Writing, review, and editing*: Diederik P. Staal, Paul M. Hendriks, Mitch C. J. van Thor, Liza D. van de Groep, Leon M. van den Toorn, Berend-Jan M. Mulder, Prewesh P. Chandoesing, Robert M. Kauling, Sanne Boerman, Annemien E. van den Bosch, Hans-Jurgen Mager, Karin A. Boomars, and Martijn C. Post. All authors read and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was performed according to the principles outlined in the Declaration of Helsinki. Informed consent was waived in accordance with Dutch national law. The study protocol was approved by the medical ethics committee of both participating centers (MEC-U, Z18.039).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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