Interstitial lung disease in patients treated with Cyclin-Dependent Kinase 4/6 inhibitors: A systematic review and meta-analysis of randomized controlled trials

Yi Zhang a,b,1, Zhuo Ma a,1, Ximu Sun b, Xin Feng b,* and Zhuoling An a, **

a Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, No 8, Gongren Tiyuchang South Road, Chaoyang District, Beijing, China
b Department of Pharmacy, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, No.17, Qi He Lou Street, Dongcheng District, Beijing, China

Abstract

Background: Cyclin-Dependent Kinase (CDK) 4/6 inhibitors have shown significant clinical activity in cancer patients. However, some concerns regarding rare adverse events (AEs) have occurred, including interstitial lung disease (ILD)/pneumonitis, for which data are deficient. The aim of this study was to evaluate the overall incidence and risk of ILD/pneumonitis related to CDK4/6 inhibitors in randomized controlled trials (RCTs).

Methods: Electronic databases and ClinicalTrials.gov were searched from inception to October 1, 2021 for RCTs reporting the occurrence of ILD/pneumonitis in cancer patients treated with CDK4/6 inhibitors. Peto odds ratios (Peto ORs) and 95% confidence intervals (CIs) were used to pool the study.

Results: 12 RCTs with a total of 16,060 patients were eligible. The overall incidence of all-grade ILD/pneumonitis was 1.6% (131/8407) in the treatment group compared with 0.7% (50/7349) in the control group. CDK4/6 inhibitors significantly increased the risk of all-grade ILD/pneumonitis with a pooled Peto OR of 2.12 (95% CI [1.57, 2.86], P<0.00001) with no heterogeneity (I²=0%). A higher incidence of grade 3 or higher ILD/pneumonitis was also observed in the treatment group (0.2%, 16/7087) compared with the control group (0.05%, 3/6617) with a Peto OR of 3.22 (95% CI [1.28, 8.09], P=0.01) with no heterogeneity (I²=0%, χ² P=0.98). A higher incidence of grade 3 or higher ILD/pneumonitis was reported in the included studies. Subgroup analyses did not show any significant difference.

Conclusions: The risk of all-grade and grade 3 or higher ILD/pneumonitis was higher in patients treated with CDK4/6 inhibitors compared to controls. The awareness for these rare AEs in the application of CDK4/6 inhibitors should be enhanced. Further studies are required to validate the mechanisms and the risk factors of ILD/pneumonitis with CDK4/6 inhibitors.

1. Introduction

In terms of new cases of cancer reported by the International Agency for Research on Cancer (IARC), breast cancer (BC) has become the most commonly diagnosed cancer in the world, with over 2.3 million new cases occurring in 2020, overtaking lung cancer [1]. Hormone receptor (HR) positive/human epidermal growth factor 2 (HER2) negative (HR+/HER2-) is the most common subtype of BC [2]. Generally, expression of HR is associated with a higher survival rate as a result of targeted endocrine therapy (ET) [3]; nevertheless, the cancer cells can produce resistance to ET, which poses an increasing therapeutic challenge for physicians [4]. The advent of CDK4/6 inhibitors have brought new hope for the treatment of HR + patients. CDK4/6 inhibitors as palbociclib, abemaciclib, ribociclib have been approved by the U.S. Food and Drug Administration (FDA) for patients with HR+/HER2- advanced or metastatic BC, and abemaciclib was also approved for early BC patients with HR+/HER2- [5-8]. Additionally, trilaciclib was the only CDK4/6 inhibitor approved for decrease the incidence of myelosuppression for lung cancer in 2021 [9].

The infrequent adverse events (AEs) were discovered with the continuously increasing use of CDK4/6 inhibitors, such as respiratory disorders. There were a few severe and fatal cases of Interstitial Lung...
Disease (ILD)/pneumonitis caused by CDK4/6 inhibitors that have been reported, which was warned by FDA in the drug labels [5–9]. The supporting data were generally from clinical trials with a low incidence of 1.0% in patients treated with palbociclib [10], [12] 3.3% in patients treated with abemaciclib [13–15], 1.1% in patients treated with ribociclib [16–18], and 0.4% in patients treated with trilaciclib [19–21]. However, isolated randomized controlled trials (RCTs) might not be sufficient to assess the overall incidence of CDK4/6 inhibitor-related ILD/pneumonitis. Meanwhile, the risk of ILD/pneumonitis related to CDK4/6 inhibitors remained undetermined.

2. Methods

2.1. Search strategy

The selection and systematic review of trials were performed following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [22]. PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, China Biology Medicine disc (CBM disc), China National Knowledge Infrastructure (CNKI), Wanfang, and ClinicalTrials.gov were searched from inception to October 1, 2021. We retrieved both Medical Subject Heading (MeSH) terms and free text words to identify relevant studies. The search terms included the keywords “CDK 4/6 inhibitor”, “Cyclin-Dependent Kinase 4/6 inhibitor”, “palbociclib”, “abemaciclib”, “ribociclib”, and “randomized controlled trial”. To identify potential unpublished data, the oncological meeting proceedings from the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the Chinese Society of Clinical Oncology (CSCO) were also searched up to October 1, 2021. The latest FDA drug labels of approved agents (palbociclib, abemaciclib, ribociclib and trilaciclib) were reviewed to identify additional relevant information. The reference list of trials and relative reviews were also searched for additional studies.

2.2. Study selection

Interstitial lung disease and pneumonitis were considered as ILD/pneumonitis events. Our selection criteria included: (a) Phase II or III RCTs with participants assigned to CDK4/6 inhibitors containing group (single agent or in combination) or non-CDK4/6 inhibitors containing controls; (b) Studies with available data reporting ILD/pneumonitis events; (c) Articles published in English or Chinese language. Case reports, reviews, case-control studies, cohort studies, phase I studies, single-arm phase II studies, RCTs without available outcomes, and RCTs with CDK4/6 inhibitors in all arms were excluded.

2.3. Data extraction and quality assessment

Two reviewers independently selected the potential trials, extracted data, and assessed the risk of bias of included trials. Another author was consulted if there was any discrepancy. The baseline demographic data, type of CDK4/6 inhibitor, type of control group, number of patients enrolled, number of patients for safety analysis, and number of patients with ILD/pneumonitis for all-grade and grade 3 or higher in the treatment and control groups were collected from the eligible studies. Included studies were assessed using the Cochrane collaboration’s tool for assessing risk of bias.

2.4. Outcomes

The primary outcomes were the incidence and risk of all-grade ILD/pneumonitis in patients treated with CDK4/6 inhibitors compared with control. All available events of ILD/pneumonitis were extracted from the latest publications first, then from ClinicalTrials.gov. The data in publication with the longest follow-up duration was used in case of various follow-up durations reported. We contacted the authors of eight relevant studies asking for further data on ILD/pneumonitis (if interested outcomes were not available from the articles, supporting information appendix or ClinicalTrials.gov). The secondary outcomes were the incidence and risk of grade 3 or higher ILD/pneumonitis. Subgroup analyses were carried out based on the study phase, type of cancer, type of CDK4/6 inhibitor, CDK4/6 inhibitor assignation (CDK4/6 inhibitor monotherapy versus combination of CDK4/6 inhibitors and other chemotherapy), type of controls and type of CDK4/6 inhibitor setting.

2.5. Statistical analysis

The results of the meta-analysis were performed using RevMan version 5.4. Due to the rare incidence of ILD/pneumonitis events, we used the Peto odds ratios (Peto ORs) with 95% confidence intervals (CIs) to pool the data. Higgins inconsistency index ($\chi^2$) test and Chi-squared ($\chi^2$) test with P value were used to evaluate heterogeneity. Significant heterogeneity between studies was defined as $\chi^2 P \leq 0.1$ or $I^2 > 50\%$. We did a sensitivity analyses by recalculating the pooled Peto OR estimates after removing one study at a time. Publication bias was assessed by the funnel plots.

3. Results

3.1. Eligible studies and characteristics

Our initial search yielded 2399 reports. After removing obvious duplicates and screening titles and abstracts, we retrieved 33 studies for full-text screening. Finally, seven publications [15,17,18,23–26] from electronic database and five RCTs from ClinicalTrials.gov [27–31] comprising 16,060 patients were included in the quantitative analysis (Fig. 1).

As was shown in Table 1, this meta-analysis included 9 phase III studies and 3 phase II studies. 9 studies were performed in patients with BC, 2 in non-small cell lung cancer (NSCLC), and 1 in head and neck cancer. Most of the studies included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Among the 12 studies, palbociclib was used in 3 trials, abemaciclib in 7 trials, and ribociclib in 2 trials. Risk of bias for each study was illustrated in supplementary appendix Figure S1. All studies reported adequate randomization, and 7 were double-blinded.

3.2. Incidence and risk of ILD/Pneumonitis

According to the 12 RCTs, the incidence of all-grade ILD/pneumonitis in patients treated with CDK4/6 inhibitors was 1.6% (131/8407) compared to 0.7% (50/7349) in the control group. CDK4/6 inhibitors significantly increased the risk of all-grade ILD/pneumonitis compared to the control group (Peto OR 2.12, 95% CI [1.57, 2.86], $P = 0.00001$, Fig. 2) with no significant heterogeneity across studies ($I^2 = 0\%$, $\chi^2 P = 0.98$). In addition, CDK4/6 inhibitors significantly increased both the risk of all-grade ILD and all-grade pneumonitis compared to the control group (Peto OR 2.23, 95% CI [1.55, 3.21], $P < 0.00001$, Figure S2 in supplementary appendix; Peto OR 1.86, 95% CI [1.07, 3.25], $P = 0.03$, Figure S3 in supplementary appendix, respectively). In terms of the risk of grade 3 or higher ILD/pneumonitis, a significant association with CDK4/6 inhibitors was observed (Peto OR 3.22, 95% CI [1.28, 8.09], $P = 0.01$, Fig. 3), with event rates of 0.2% (16/7087) in the treatment group and 0.05% (3/6617) in the control group with no significant heterogeneity across studies ($I^2 = 0\%$, $\chi^2 P = 0.62$).

3.3. Subgroups analyses

We listed the incidence and risk of all-grade CDK4/6 inhibitor-related ILD/pneumonitis in the subgroups in Table 2. Higher Peto ORs of all-grade ILD/pneumonitis associated with CDK4/6 inhibitors were...
observed among trials of BC (Peto OR 2.24, 95% CI [1.63, 3.06]), combination therapy (Peto OR 2.22, 95% CI [1.63, 3.02]), phase III trials (Peto OR 2.16, 95% CI [1.58, 2.94]), endocrine therapy as control group (Peto OR 2.24, 95% CI [1.63, 3.07]), and CDK4/6 inhibitors as adjuvant therapy (Peto OR 2.28, 95% CI [1.61, 3.24]) compared to the trials of other cancer type, monotherapy, phase II trials, other control groups and other settings for CDK4/6 inhibitors. But none of the differences between these subgroups were statistically significant.

Stratified by types of CDK4/6 inhibitors, the incidence of all-grade ILD/pneumonitis in patients treated with palbociclib, abemaciclib and ribociclib was 0.5% (16/3348), 2.5% (108/4397), and 1.1% (7/662), respectively. Compared with the control group, palbociclib and abemaciclib significantly increased the risk of CDK4/6 inhibitor-related ILD/pneumonitis (Peto OR 2.41, 95% CI [1.04, 5.59], \(P = 0.04\); Peto OR 2.10, 95% CI [1.51, 2.92], \(P < 0.00001\); respectively), while a similar risk was found between ribociclib and the control group (Peto OR 1.77, 95% CI [0.44, 7.10], \(P = 0.42\)). However, the test for subgroup differences suggested that there was no statistically significant subgroup effect (\(P = 0.92\)).

3.4. Sensitivity analyses and publication bias

Sensitivity analyses were performed to assess the stability of the meta-analysis. The exclusion of studies one by one did not result in significant alterations in outcomes (Table S1 in the supplementary appendix). There was no detectable asymmetry in the funnel plot suggesting a low risk of publication bias in our meta-analysis (Figure S4 in the supplementary appendix).

4. Discussion

To the best of our knowledge, this is the latest and most comprehensive meta-analysis to provide an evaluation of the incidence and risk of all-grade and grade 3 or higher ILD/pneumonitis in cancer patients treated with CDK4/6 inhibitors.

The efficacy of CDK4/6 inhibitors has been verified in several RCTs [10-18] primarily in patients with metastatic HR+/HER2- BC. According to the FDA drug labels, palbociclib, abemaciclib, and ribociclib can be used in combination with aromatase inhibitor or fulvestrant for HR+/HER2-advanced or metastatic BC patients, while only abemaciclib is available as monotherapy [5-7]. In addition, abemaciclib was approved by the FDA in 2021 with ET for adjuvant treatment of HR+/HER2-early BC patients with high risk of recurrence and a Ki-67 score \(\geq 20\%\) [8]. Trilaciclib can be used to decrease the incidence of myelosuppression for small cell lung cancer [9]. Furthermore, CDK4/6 inhibitors have shown consistent activity in preclinical models such as colon cancer [32-34] glioblastoma [35,36], prostate carcinoma, sarcomas [37-41], pancreatic ductal adenocarcinoma, melanoma, NSCLC, head and neck cancer and esophageal adenocarcinoma [42]. Considering the potential clinical use of CDK4/6 inhibitors, a thorough understanding of all associated toxicities is necessary to ensure that patients can achieve maximal clinical benefits with minimum risks. In general, CDK4/6 inhibitors are well-tolerated agents with predictable AEs [43]. Hematological toxicities such as neutropenia were especially
| NCT number | Phase | Cancer type | ECOG | CDK4/6 inhibitor | Patients enrolled | Patient groups | Age | ILD/pneumonitis events | Events reported |
|------------|-------|-------------|------|-----------------|-------------------|----------------|-----|------------------------|-----------------|
| NCT 02513394 | III | BC | 0–1 | Palbociclib | 5760 | Palbociclib 125 mg qd + ET (n = 2883) versus ET (n = 2877) | 52 (45–61) | 2840 | 2930 | 13 | 5 | 1 | 0 | Publication |
| NCT 03155997 | III | BC | 0–1 | Abemaciclib | 5637 | Abemaciclib 150 mg bid + ET (n = 2808) versus ET (n = 2829) | 51 (23–89) | 2791 | 2800 | 76 | 33 | 10 | 1 | Publication |
| NCT 02675231 | II | BC | 0–1 | Abemaciclib | 237 | Abemaciclib 150 mg bid + Trastuzumab + Fulvestrant (n = 79) versus Standard chemotherapy + Trastuzumab (n = 79) | 55 (47–62) | 78 | 72 | 3 | 1 | 1 | 1 | Publication |
| NCT 02763566 | III | BC | 0–1 | Abemaciclib | 463 | Abemaciclib 150 mg bid + NSAI (n = 207) versus Placebo + NSAI (n = 99) | 54 (32–83) | 207 | 99 | 13 | 3 | 1 | 1 | Publication |
| NCT 02422615 | III | BC | 0–1 | Ribociclib | 726 | Ribociclib 600 mg qd + NSAI (n = 484) versus Placebo + NSAI (n = 242) | 63 (31–89) | 327 | 161 | 6 | 2 | 1 | 0 | Publication |
| NCT 02278120 | III | BC | 0–1 | Ribociclib | 672 | Ribociclib 600 mg qd + NSAI/Tamoxifen + Goserelin (n = 335) versus Placebo + NSAI/Tamoxifen + Goserelin (n = 337) | 43 (25–58) | 335 | 337 | 1 | 0 | 0 | 0 | Publication |
| NCT 02246621 | III | BC | 0–1 | Abemaciclib | 493 | Abemaciclib 150 mg bid + NSAI (n = 328) versus Placebo + NSAI (n = 165) | 63 (38–87) | 328 | 165 | 1 | 0 | 1 | 0 | Publication |
| NCT 01740427 | III | BC | 0–2 | Palbociclib | 666 | Palbociclib 125 mg bid + Letrozole (n = 444) versus Placebo + Letrozole (n = 222) | 61.7 | 444 | 222 | 2 | 0 | 2 | 0 | ClinicalTrials.gov |
| NCT 02107703 | III | BC | 0–1 | Abemaciclib | 669 | Abemaciclib 150 mg bid + Fulvestrant (n = 446) versus Placebo + Fulvestrant (n = 223) | 59.9 | 441 | 223 | 4 | 0 | 4 | 0 | ClinicalTrials.gov |
| NCT 02499120 | II | Head and neck | NA | Palbociclib | 125 | Palbociclib 125 mg qd + Cetuximab (n = 665) versus Placebo + Cetuximab (n = 60) | 59.5 | 64 | 60 | 1 | 1 | 1 | 1 | ClinicalTrials.gov |
| NCT 02450539 | II | NSCLC | 0–1 | Abemaciclib | 159 | Abemaciclib 200 mg bid (n = 106) versus Docetaxel (n = 53) | 63.5 | 106 | 52 | 3 | 1 | 3 | 1 | ClinicalTrials.gov |
| NCT 02152631 | III | NSCLC | 0–1 | Abemaciclib | 453 | Abemaciclib 200 mg bid (n = 270) versus Erlotinib (n = 183) | 62.5 | 265 | 175 | 4 | 3 | 4 | 3 | ClinicalTrials.gov |

Abbreviation: ECOG, Eastern Cooperative Oncology Group; SAEs, severe adverse events; T, treatment group; C, control group; BC, breast cancer; NSCLC, non-small cell lung cancer; qd, once daily; bid, twice daily; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor; NA, not available.
associated with palbociclib and ribociclib, whereas abemaciclib showed a high rate of gastrointestinal toxicities such as diarrhea and ribociclib was associated with a high rate of liver injury and QTc prolongation \[43, 44\]. Besides, increased thromboembolic events associated all CDK4/6 inhibitors have attracted clinical attention \[45\]. The major side effects associated with CDK4/6 inhibitors are similar, including neutropenia and gastrointestinal side effects \[43, 46, 47\]. With the continuously increasing use of CDK4/6 inhibitors, several cases of ILD/pneumonitis associated with palbociclib and ribociclib, whereas aberrmaticinib showed a high rate of gastrointestinal toxicities such as diarrhea and ribociclib was associated with a high rate of liver injury and QTc prolongation \[43, 44\]. Besides, increased thromboembolic events associated all CDK4/6 inhibitors have attracted clinical attention \[45\]. The major side effects associated with CDK4/6 inhibitors are similar, including neutropenia and gastrointestinal side effects \[43, 46, 47\]. With the continuously increasing use of CDK4/6 inhibitors, several cases of ILD/pneumonitis...
related to these agents have been reported, indicating a potential association between CDK4/6 inhibitors and ILD/pneumonitis [48–53].

Our meta-analysis demonstrated a significantly increased risk of all-grade ILD/pneumonitis related to CDK4/6 inhibitors compared to the control group. According to a pharmacovigilance assessment study, CDK4/6 inhibitors were detected with signals of ILD as a class compared to all other drugs in the FDA Adverse Event Reporting System (FAERS) database, corresponding to reporting odds ratio (ROR) 1.50 (95% CI [1.28, 1.74]) [44]. The significantly increased risk of grade 3 or higher CDK4/6 inhibitors were detected with signals of ILD as a class compared to CDK4/6 inhibitors might result in serious outcomes in clinical practice. Of 117 patients who reported ILD/pneumonitis, 14 (12.0%) were grade 3 and 4, and 2 (1.7%) resulted in death with abemaciclib [12,24]. However, death was recorded in 29% (46/161) of CDK4/6 inhibitors-related ILD/pneumonitis cases in the real-world study [44]. Several reasons might explain the discrepancy. First, AEs reported in ClinicalTrials.gov were not classified according to the Common Terminology Criteria for Adverse Events (CTCAE) [54], resulting in missing reports of deaths. Second, insufficient follow-up duration might lead to an underestimation of mortality.

In the subgroup analyses, the higher Peto ORs of all-grade ILD/pneumonitis were found in phase III trials, BC patients, patients treated with abemaciclib and palbociclib, patients treated with CDK4/6 inhibitor in combination with other chemotherapy, endocrine therapy as control group, and CDK4/6 inhibitors as adjuvant treatment but none of these differences was statistically significant. Phase II trials, patients with other cancers, patients treated with ribociclib, and CDK4/6 inhibitors monotherapy might not have enough power to detect or rule out the differences due to the small sample size of these subgroups. Moreover, these subgroup analyses were performed for exploratory purposes only, and no definitive conclusions should be drawn. Studies based on individual patient data and large clinical trials are needed to determine the risk factors for the development of CDK4/6 inhibitor-related ILD/pneumonitis.

Among different CDK4/6 inhibitors, abemaciclib and palbociclib were noted to be statistically significantly associated with ILD/pneumonitis with Peto OR 2.10 (P < 0.00001) and 2.41 (P = 0.04), respectively. This finding was consistent with previous pharmacovigilance assessment study [55], in which the significant pharmacovigilance signals were found with abemaciclib and palbociclib (ROR 4.8, 95% CI [3.8, 6.1]; ROR 1.3, 95%CI [1.1, 1.4], respectively). It is speculated that abemaciclib may cause more AEs through the following points. First, compared with palbociclib and ribociclib, abemaciclib possesses unique pharmacological properties [44]. Second, abemaciclib exhibits a wider selectivity towards other CDKs and kinases, i.e., it has a low specificity for CDK4/6 [43,55–57]. Third, abemaciclib acts through other mechanisms of action in addition to inducing G1 cell cycle arrest, meaning that it may act independently of the CDK4/6-cyclin D-RB pathway [56, 58–60]. Therefore, the potential toxicity of abemaciclib is presumed to be greater by the differences between abemaciclib and the other two CDK4/6 inhibitors.

The mechanisms of CDK4/6 inhibitor-related ILD/pneumonitis are still unclear. An in vivo study suggested that palbociclib augmented inflammatory cell recruitment (including macrophages and T cells) in the bronchoalveolar lavage fluid, which could be a consequence of the palbociclib-induced cell cycle arrest with relevant cellular senescence [44,61]. It was further proposed that in the presence of cell cycle inhibitor like palbociclib, the inflammatory cell milieu was altered, which could leading to cell senescence [51,62]. This speculation might explain the reason why CDK4/6 inhibitors caused lung injury.

In addition, previous real-world study based on the FAERS database showed that a median latency of 63 days (range 21–136) for CDK4/6 inhibitor-associated ILD [44]. This finding was in line with the results from an adverse event-time analysis of abemaciclib and palbociclib using data from Japanese Adverse Drug Event Report (JADER) database, suggesting that both abemaciclib and palbociclib were associated with the onset of ILD after 1–2 months from the start of treatment [55]. A retrospective study of drug-induced ILD demonstrated that, there was a certain similar trend in the timing of the occurrence of ILD induced by most anticancer drugs, most of which occurred within 3 months [63].

Our study has several limitations. First, five studies included were open-label, introducing high chances of performance bias and detection bias. Second, the severity of ILD/pneumonitis events was defined differently from electronic databases and ClinicalTrials.gov, with seven studies classified by the CTCAE [54], whereas the others classified by all AEs and severe adverse events (SAEs). Third, data were extracted from clinical trial results, and individual information on patient with ILD/pneumonitis was not available. Therefore, the potential risk factors for developing ILD/pneumonitis were not included in our study. Fourth, studies included were not specifically designed to assess the AEs, which might lead to an underestimation of ILD/pneumonitis related to CDK4/6 inhibitors. Finally, trials included were performed from multicenter, where the diagnostic criteria of ILD/pneumonitis and the ability to detect these events might be different. However, the strength of our study was that we set strict selection criteria with the most comprehensive studies included from both electronic databases and ClinicalTrials.gov, and the heterogeneity among included studies was low.

5. Conclusion

Our study demonstrated that patients treated with CDK 4/6 inhibitors had a higher risk of all-grade and grade 3 or higher ILD/pneumonitis compared to the control group. CDK4/6 inhibitor-related ILD/pneumonitis events are rare but may be life-threatening, which should attract clinical attention. Future studies are required to confirm the mechanism and explore the possible risk factors.

Author contributions

The data acquisition, statistical analysis, article drafting and revising were performed by Zhuo Ma and Yi Zhang. Xin Feng and Zhuoling An conceived and supervised the study. The final manuscript was read, checked and approved by all authors.

Funding source

None.

Ethical approval

None.

Declaration of competing interest

All authors have no significant disclosures.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.02.011.

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