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CDK4/6 Inhibitor–Associated Drug-Induced Liver Injury: Clinical Characteristics, Management, and Rechallenge Outcomes—A Systematic Review

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Abstract. CDK4/6 inhibitor–associated drug-induced liver injury (DILI) is an uncommon but clinically important adverse event that may necessitate treatment interruption or discontinuation.This study aimed to systematically characterizethe clinical features, management, and rechallenge outcomes of CDK4/6 inhibitor–associated DILI through a pooled analysis of reported cases. Literature was retrieved from PubMed, Google Scholar, China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Journal Database, J-STAGE, and relevant conference sources, and patient characteristics, biochemical findings, treatment patterns, and outcomes were systematically extracted and analyzed. A total of 62 patients from 37 eligible studies were included. Ribociclib was the most frequently implicated agent (56.5%), followed by abemaciclib (32.3%). The median time to DILI onset was 57 days (IQR 29–74), and 98.2% of patients with available grading data developed grade 3 or higher liver injury. Despite the severity of reported cases, 90.3% of patients recovered. Among 39 patients with clearly reported rechallenge outcomes, recurrent DILI occurred in 41.0%. Recurrence was substantially more frequent after same-drug rechallenge than after switching to an alternative CDK4/6 inhibitor (81.3% vs. 13.0%, $p<0.001$), whereas no baseline clinical or biochemical variables were significantly associated with DILI recurrence in the exploratory analyses.Overall, CDK4/6 inhibitor–associated DILI can be clinically severe but is frequently reversible after drug withdrawal. Switching to an alternative CDK4/6 inhibitor after complete recovery may represent a potential management strategy in selected patients, although further prospective studies are required to evaluate the safety of this strategy.

Keywords: CDK4/6 inhibitors, Drug-induced liver injury, Hepatotoxicity, Rechallenge strategy, Hormone receptor-positive breast cancer

1. Introduction

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have significantly changed the treatment paradigm of hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−) breast cancer. CDK4/6 inhibitors suppress CDK4/6-mediated phosphorylation of retinoblastoma protein (Rb), thereby maintaining Rb-mediated inhibition of E2F and inducing G1

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cell-cycle arrest, which ultimately inhibits tumour cell proliferation [1]. Palbociclib, ribociclib, and abemaciclib are widely used in combination with endocrine therapy for advanced HR+/HER2− breast cancer. More recently, the clinical application of CDK4/6 inhibitors has expanded into the early-stage setting, with the monarchE and NATALEE trials demonstrating benefits of adjuvant abemaciclib and ribociclib, respectively, in selected patients with HR+/HER2− early breast cancer [2, 3]. Although CDK4/6 inhibitors are generally manageable in clinical practice, treatment-related adverse events include neutropenia, gastrointestinal toxicity such as diarrhoea, QTc prolongation, and hepatotoxicity, with toxicity profiles differing among individual agents [4].

Drug-induced liver injury (DILI) is a clinically relevant adverse event associated with CDK4/6 inhibitor therapy. Its clinical presentation may range from asymptomatic elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to clinically significant hepatitis and hyperbilirubinaemia, with severe liver injury occurring in a small proportion of patients [5]. The risk of hepatotoxicity appears to differ among individual CDK4/6 inhibitors. Recent real-world data showed that DILI occurred more frequently with ribociclib and abemaciclib than with palbociclib, with reported incidences of 8.3%, 6.7%, and 1.4%, respectively [5]. Consistent with these findings, a systematic review and pharmacovigilance analysis also identified stronger hepatic safety signals for ribociclib and abemaciclib, whereas palbociclib showed a comparatively lower hepatotoxicity signal [6]. Therefore, characterization of CDK4/6 inhibitor-associated DILI is important for treatment monitoring, early recognition of liver injury, and clinical decision-making.

However, the clinical course and optimal management of CDK4/6 inhibitor-associated DILI remain incompletely defined. Reported cases show considerable heterogeneity in time to onset, biochemical pattern, severity, histopathological findings, and treatment response [5]. Corticosteroids have occasionally been used in persistent or severe cases, although their clinical benefit remains uncertain [7]. In addition, the safety of rechallenge with the same agent or switching to another CDK4/6 inhibitor remains unclear, as both successful retreatment and recurrent liver injury have been reported [5].

Previous studies have largely focused on overall hepatotoxicity risk, liver enzyme abnormalities in clinical trials, or pharmacovigilance signals, whereas patient-level clinical characteristics and management outcomes, particularly outcomes after rechallenge or switching between CDK4/6 inhibitors, remain incompletely characterized. Therefore, this systematic review aims to characterize reported cases of CDK4/6 inhibitor-associated DILI, including patient characteristics, implicated agents, time to onset, biochemical and clinical patterns, severity, management, recovery, and outcomes after corticosteroid treatment, rechallenge, or switching to another CDK4/6 inhibitor. By integrating these patient-level data, this study seeks to provide clinically relevant evidence to support the recognition and management of this rare but potentially serious adverse drug reaction.

2. Methods

Literature was systematically searched in PubMed, Google Scholar, China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Chinese Science and Technology Journal Database, and J-STAGE. Supplementary searches were conducted in relevant publisher databases and conference abstract archives, including AACR/SABCS, the Japanese Breast Cancer Society, and the Japanese Society of Hepatology. The databases were searched from inception to September 1, 2026. Search terms included "CDK4/6 inhibitor," "cyclin-dependent kinase 4/6 inhibitor," "palbociclib," "ribociclib," "abemaciclib," "dalpiciclib," "drug-induced liver injury," "hepatotoxicity," "hepatitis," "liver dysfunction," "transaminase elevation," and their corresponding Chinese and Japanese terms. Full-text articles and eligible conference abstracts were reviewed individually for inclusion.

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Duplicate publications and review articles without original patient-level data were excluded. Where multiple publications described the same patient, the most complete report was retained to avoid duplicate inclusion. Thirty-seven eligible studies were included, with a total of 62 patients [8-44].

For the purposes of this review, cases were included when clinically significant liver injury was temporally associated with CDK4/6 inhibitor exposure and was considered treatment-related by the original authors. Most cases represented conventional DILI, whereas reports involving distinct mechanisms, including HBV reactivation, pseudocirrhosis, or vascular liver injury, were retained as clinically relevant CDK4/6 inhibitor–associated hepatic injuries.

A standardized data extraction form developed in Microsoft Excel was used to collect patient-level information, including age, sex, cancer type, CDK4/6 inhibitor type, time to onset of liver injury, peak ALT, AST, ALP, and total bilirubin levels, CTCAE grade, jaundice, treatment discontinuation, corticosteroid use, recovery, rechallenge or switching strategy, and recurrence of DILI after rechallenge. Time to DILI onset was standardized to days when sufficient information was available. Total bilirubin values reported in alternative units were converted to mg/dL. Rechallenge strategy was classified according to the first CDK4/6 inhibitor administered after recovery from the initial DILI episode. The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Case Reports and Case Series, as appropriate. Each item was rated as "Yes," "No," "Unclear," or "Not applicable." Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median and interquartile range [M (Q1, Q3)]. Comparisons between two groups were performed using the Mann–Whitney U test for continuous variables, while categorical variables were compared using Fisher's exact test. Missing data were excluded from the corresponding analyses, and percentages were calculated using available-case denominators. A two-sided p value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and clinical features

A total of 62 patients from 37 eligible studies were included. Their clinical characteristics and outcomes are summarized in Table 1.

Table 1. Clinical characteristics and outcomes of patients with CDK4/6 inhibitor–associated DILI

	Available number	Result
Gender		
Female	62	(62/62) 100%
Age	45	58.5 ± 11.9
Cancer type		
Breast cancer	62	(62/62) 100%
CDK4/6 inhibitor		
Ribociclib	62	(35/62) 56.5%
Abemaciclib	62	(20/62) 32.3%
Palbociclib	62	(6/62) 9.7%

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Table 1. (continued)

Dalpiciclib	62	(1/62) 1.6%
Clinical characteristics and outcomes		
Time to DILI onset	38	57 (IQR 29–74)
Peak ALT, U/L	40	838.5 (IQR 512.5–1371.3)
Peak AST, U/L	32	693.0 (IQR 337.5–1053.5)
Peak ALP, U/L	20	173.0 (IQR 126.8–286.5)
Peak total bilirubin, mg/dL	25	4.6 (IQR 1.5–7.9)
CTCAE grade ≥3	57	56/57 (98.2%)
Jaundice	38	15/38 (39.5%)
Corticosteroid treatment	55	24/55 (43.6%)
CDK4/6 inhibitor discontinued	60	60/60 (100%)
Recovery	62	56/62 (90.3%)
Rechallenge/switching performed	62	44/62 (71.0%)
DILI recurrence after rechallenge	39	16/39 (41.0%)
Death during reported follow-up	62	6/62 (9.7%)

In Table 1, a total of 62 patients with CDK4/6 inhibitor–associated drug-induced liver injury (DILI) were included in this study. All patients were female and had breast cancer. Among the 45 patients with exact age data available, the mean age was 58.5 ± 11.9 years. Ribociclib was the most frequently implicated CDK4/6 inhibitor, accounting for 35 cases (56.5%), followed by abemaciclib in 20 cases (32.3%), palbociclib in 6 cases (9.7%), and dalpiciclib in 1 case (1.6%).

Among patients with clearly reported onset data, the median time to DILI onset was 57 days (IQR 29–74 days). Liver biochemical abnormalities were marked, with a median peak ALT of 838.5 U/L (IQR 512.5–1371.3 U/L) and a median peak AST of 693.0 U/L (IQR 337.5–1053.5 U/L). The median peak ALP was 173.0 U/L (IQR 126.8–286.5 U/L), while the median peak total bilirubin was 4.6 mg/dL (IQR 1.5–7.9 mg/dL).

Among the 57 patients with available CTCAE grading data, 56 (98.2%) developed grade 3 or higher liver injury. Of the 38 patients with available information on jaundice, 15 (39.5%) developed jaundice. Corticosteroid treatment was administered in 24 of 55 patients (43.6%) with available treatment information. Among the 60 patients with available data on treatment discontinuation, all discontinued the implicated CDK4/6 inhibitor. Overall, 56 patients (90.3%) recovered from the liver injury.

In addition, 44 patients (71.0%) underwent rechallenge with the same CDK4/6 inhibitor or switched to another CDK4/6 inhibitor after recovery. Among the 39 patients with clearly reported rechallenge outcomes, recurrent DILI occurred in 16 patients (41.0%), whereas 23 patients (59.0%) did not experience recurrence. Six patients (9.7%) died during the reported follow-up; however, the available case reports did not establish that all deaths were directly attributable to DILI.

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3.2. Comparison between ribociclib- and abemaciclib-associated DILI

As shown in Table 2, patients with ribociclib-associated DILI were younger than those with abemaciclib-associated DILI, with a median age of 54.5 years (IQR 44.5–66.8) versus 65.5 years (IQR 55.8–71.3), respectively (p=0.040). No significant differences were observed between the two groups in time to DILI onset, peak ALT, peak AST, peak total bilirubin, the proportion of grade ≥4 liver injury, jaundice, corticosteroid use, or recovery (all p>0.05).

Rechallenge or switching to another CDK4/6 inhibitor was more frequently reported in the ribociclib group than in the abemaciclib group (85.7% vs. 60.0%, p=0.048). However, among patients with available rechallenge outcomes, the rate of recurrent DILI was similar between the two groups (36.0% vs. 41.7%, p=1.000). Overall, aside from differences in age and the frequency of rechallenge, the biochemical severity, clinical manifestations, and short-term outcomes of reported ribociclib- and abemaciclib-associated DILI cases were broadly comparable.

Table 2. Comparison of clinical characteristics between ribociclib- and abemaciclib-associated DILI

	Ribociclib (n=35)	Abemaciclib (n=20)	P value
Age	54.5 (44.5–66.8), n=22	65.5 (55.8–71.3), n=16	0.040
Time to onset, days	56.0 (30.0–60.0), n=13	57.5 (29.8–62.5), n=20	0.472
Peak ALT, U/L	829 (566–1797.5), n=19	848 (493–1199), n=17	0.267
Peak AST, U/L	709.5 (278–1267.5), n=16	672 (421.5–828), n=11	0.639
Peak total bilirubin, mg/dL	4.0 (2.2–6.5), n=12	3.9 (1.4–6.7), n=10	0.895
Grade ≥4 liver injury	16/30 (53.3%)	10/20 (50.0%)	1.000
Jaundice	6/19 (31.6%)	6/13 (46.2%)	0.473
Corticosteroid treatment	16/30 (53.3%)	7/20 (35.0%)	0.254
Recovery	33/35 (94.3%)	19/20 (95.0%)	1.000
Rechallenge/switching performed	30/35 (85.7%)	12/20 (60.0%)	0.048
Recurrence after rechallenge	9/25 (36.0%)	5/12 (41.7%)	1.000

3.3. Comparison between patients with and without recurrent DILI after rechallenge

In Table 3, among the 39 patients with clearly reported rechallenge outcomes, recurrent DILI occurred in 16 patients, whereas 23 patients did not experience recurrence. As shown in Table 3, there were no significant differences between the recurrence and no-recurrence groups in age, initial CDK4/6 inhibitor, time to initial DILI onset, peak ALT, peak AST, peak total bilirubin, grade ≥4 initial liver injury, jaundice, or corticosteroid treatment (all p>0.05).

Table 3. Comparison between patients with and without recurrent DILI after rechallenge

	Recurrence (n=16)	No recurrence (n=23)	P value
Age	57.0 (48.0–65.5), n=15	63.0 (54.8–68.8), n=16	0.243
Initial CDK4/6 inhibitor			0.298

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Table 2. (continued)

Ribociclib	9/16 (56.3%)	16/23 (69.6%)	
Abemaciclib	5/16 (31.3%)	7/23 (30.4%)	
Palbociclib	2/16 (12.5%)	0/23 (0%)	
Time to initial DILI onset, days	57.0 (28.0–90.0), n=13	42.5 (29.0–60.3), n=12	0.624
Peak ALT, U/L	795.5 (633.5–1320.5), n=14	1073 (414–1400), n=13	0.942
Peak AST, U/L	454.0 (337.5–655.3), n=12	993.5 (703.5–1267.5), n=8	0.083
Peak total bilirubin, mg/dL	2.03 (0.85–4.80), n=7	4.30 (2.00–5.87), n=8	0.271
Grade ≥4 initial liver injury	8/16 (50.0%)	11/23 (47.8%)	1.000
Jaundice	3/14 (21.4%)	3/12 (25.0%)	1.000
Corticosteroid treatment	7/16 (43.8%)	9/23 (39.1%)	1.000

3.4. Comparison of same-drug rechallenge and switching strategies

In Table 4, among the 39 patients with clearly reported rechallenge outcomes, 16 were rechallenged with the same CDK4/6 inhibitor and 23 were switched to an alternative CDK4/6 inhibitor. As shown in Table 4, recurrent DILI occurred in 13 of 16 patients (81.3%) who underwent same-drug rechallenge, compared with 3 of 23 patients (13.0%) who switched to another CDK4/6 inhibitor ($p<0.001$). Conversely, the proportion of patients without recurrent liver injury was substantially higher in the switching group than in the same-drug rechallenge group (87.0% vs. 18.8%).

Among specific switching strategies, recurrence was reported in 3 of 15 patients (20.0%) who switched from ribociclib to palbociclib, whereas no recurrent DILI was reported among the limited number of patients who switched from abemaciclib to palbociclib or from ribociclib to abemaciclib. Overall, switching to an alternative CDK4/6 inhibitor was associated with a markedly lower proportion of recurrent DILI than rechallenge with the original agent. However, the small numbers within individual switching pathways should be considered when interpreting these findings.

Table 4. DILI recurrence according to CDK4/6 inhibitor rechallenge strategy

Rechallenge strategy	Total, n	Recurrent DILI, n (%)	No recurrence, n (%)	P value
Same-drug rechallenge	16	13 (81.3%)	3 (18.8%)	<0.001
Switch to another CDK4/6 inhibitor	23	3 (13.0%)	20 (87.0%)	
Ribociclib → Palbociclib	15	3 (20.0%)	12 (80.0%)	—
Abemaciclib → Palbociclib	6	0 (0%)	6 (100%)	—
Ribociclib → Abemaciclib	2	0 (0%)	2 (100%)	—

The p value represents the comparison of DILI recurrence between same-drug rechallenge and switching to an alternative CDK4/6 inhibitor using Fisher's exact test. Individual switching pathways were not statistically compared because of the small sample sizes.

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4. Discussion

Based on 62 reported cases from 37 studies, this systematic review provides a patient-level characterization of CDK4/6 inhibitor–associated drug-induced liver injury (DILI), with particular emphasis on clinical presentation, management, and outcomes after rechallenge. The findings demonstrate that reported cases were predominantly associated with ribociclib and abemaciclib, with a median time to DILI onset of approximately 2 months. Liver injury was frequently severe among published cases, with 98.2% of patients with available grading data experiencing grade 3 or higher toxicity. Despite this severity, most patients recovered following drug discontinuation and supportive or pharmacological management. Importantly, the present analysis identified a strong association between rechallenge strategy and recurrent DILI: recurrence was substantially more frequently reported after rechallenge with the original CDK4/6 inhibitor than after switching to an alternative agent.

One of the major clinical characteristics observed in this study was the marked biochemical severity of reported CDK4/6 inhibitor–associated DILI. Median peak ALT and AST levels were 838.5 U/L and 693.0 U/L, respectively, while almost all patients with available CTCAE grading data had grade 3 or higher liver injury. Jaundice was also reported in 39.5% of patients with available information. These findings demonstrate that clinically significant liver injury has been reported in association with CDK4/6 inhibitor therapy. The high proportion of severe cases should be interpreted in light of the characteristics of the available literature. Most included studies were case reports or small case series, which tend to describe more unusual or severe adverse events, while mild or transient liver enzyme abnormalities are less likely to be reported. The proportion observed in this review therefore should not be taken as representative of the incidence or severity pattern of hepatotoxicity in the wider population receiving CDK4/6 inhibitors. Clinical trial and real-world data indicate that clinically significant hepatotoxicity occurs in only a subset of patients receiving CDK4/6 inhibitors, with the reported hepatic risk differing among individual agents [5, 6].

The median interval from treatment initiation to DILI was 57 days, although the timing varied considerably between cases. Most events occurred within the first few months of therapy, making this an important period for liver biochemical monitoring. Some cases developed later, however, indicating that the risk is not confined to the initial treatment cycles. Early normal liver tests therefore do not rule out liver injury developing later during CDK4/6 inhibitor treatment.

Ribociclib accounted for more than half of the reported cases in this review, followed by abemaciclib, whereas relatively few cases were associated with palbociclib. This distribution is broadly consistent with previous pharmacovigilance and real-world studies suggesting stronger hepatic safety signals for ribociclib and abemaciclib than for palbociclib [5]. However, the distribution of published cases cannot be used to estimate comparative incidence because the number of patients exposed to each agent, prescribing patterns, regional differences, and reporting behaviour were not available. Therefore, the predominance of ribociclib cases in the present dataset should be interpreted as a characteristic of the published literature rather than direct evidence that ribociclib has a specific magnitude of excess risk.

Comparison between ribociclib- and abemaciclib-associated DILI demonstrated broadly similar biochemical severity and short-term clinical outcomes. No significant differences were observed in time to onset, peak ALT, peak AST, peak bilirubin, grade ≥4 liver injury, jaundice, corticosteroid use, recovery, or recurrence following rechallenge. Patients with ribociclib-associated DILI were younger, and rechallenge was more frequently reported in this group. Although both comparisons reached nominal statistical significance, these findings should be interpreted cautiously because of

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the small sample size, multiple comparisons, and case-report-based design, and should not be regarded as definitive evidence of drug-specific clinical phenotypes. Rather, the overall similarity between the two groups suggests that once clinically apparent DILI develops, its biochemical and clinical manifestations may overlap substantially across different CDK4/6 inhibitors.

Another notable finding was the frequent use of corticosteroids. Among patients with available treatment information, 43.6% received corticosteroid therapy. Previous reports have described corticosteroid treatment particularly in persistent, severe, or autoimmune-like cases, although its clinical benefit remains uncertain [7, 28]. In the present study, corticosteroid use did not differ significantly between patients who subsequently experienced recurrent DILI and those who did not. These data do not establish whether corticosteroids improve clinical outcomes. Patients with more severe or persistent liver injury were probably more likely to receive steroid treatment, which introduces confounding by indication. Steroid dose and recovery time were also inconsistently reported. Corticosteroid use therefore remains a case-specific decision, particularly in patients with persistent biochemical abnormalities or possible immune-mediated liver injury.

Management after recovery from the initial liver injury was a key focus of this analysis. Overall, 71.0% of patients underwent either rechallenge with the same CDK4/6 inhibitor or switching to another agent. Among those with evaluable outcomes, 41.0% developed recurrent DILI. Recurrence rates did not differ significantly according to age, the initially implicated CDK4/6 inhibitor, time to DILI onset, peak ALT, AST or bilirubin, initial severity, jaundice, or corticosteroid use. Taken together, the available baseline clinical and biochemical features did not clearly distinguish patients who later developed recurrent liver injury after treatment was resumed.

In contrast, a strong association was observed between the rechallenge strategy and recurrent DILI. Recurrent liver injury occurred in 13 of 16 patients (81.3%) rechallenged with the same CDK4/6 inhibitor, compared with only 3 of 23 patients (13.0%) who switched to an alternative CDK4/6 inhibitor. Conversely, 87.0% of patients who switched to another CDK4/6 inhibitor did not experience recurrent liver injury, compared with only 18.8% of those rechallenged with the original drug. Among specific switching strategies, recurrence was reported in 3 of 15 patients who switched from ribociclib to palbociclib, whereas no recurrent DILI was reported among the smaller numbers who switched from abemaciclib to palbociclib or from ribociclib to abemaciclib.

These findings raise the possibility that clinically significant hepatotoxicity may not necessarily represent complete cross-toxicity across the CDK4/6 inhibitor class. In selected patients who continue to require CDK4/6 inhibition, switching to an alternative agent after complete biochemical recovery may therefore represent a potential management strategy. Nevertheless, this result requires particularly cautious interpretation. Treatment allocation was not random, and clinicians may have preferentially selected switching for patients considered suitable for further therapy while avoiding rechallenge in patients with the most severe initial toxicity. In addition, successful switching may be more likely to be published than unsuccessful attempts. Therefore, the present study demonstrates an association between switching and a lower proportion of reported recurrent DILI, but cannot establish that switching is intrinsically safer than same-drug rechallenge.

Despite the severity of many reported cases, 90.3% of patients recovered. All patients with available discontinuation data stopped the implicated CDK4/6 inhibitor. Six deaths were reported during follow-up, although the available reports did not consistently attribute these deaths directly to DILI. Mortality in this review should therefore be considered all-cause rather than DILI-specific. Clearer reporting of the cause of death would be useful in future studies.

The mechanisms underlying CDK4/6 inhibitor–associated DILI remain incompletely understood and may differ among individual agents. Proposed mechanisms include the formation of reactive or

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immunogenic metabolites, oxidative stress, inhibition of hepatobiliary transporters such as the bile salt export pump (BSEP), and immune-mediated hepatic injury. Drug–drug interactions involving CYP3A4 may also increase drug exposure and susceptibility to hepatotoxicity [45, 46]. However, these mechanisms remain incompletely validated and require further experimental and clinical investigation.

A key strength of this review was the use of patient-level data, which allowed the timing, severity, management, recovery, and outcomes after treatment resumption to be examined together. The search also covered English, Chinese, and Japanese literature as well as relevant conference abstracts, broadening the range of cases identified. Rechallenge and switching outcomes were analysed separately, and patients with and without recurrent DILI were compared to explore possible clinical factors associated with recurrence.

Several limitations should also be acknowledged. First, the evidence was predominantly derived from case reports and small case series, making the analysis highly susceptible to publication and reporting bias. Severe, unusual, or successfully managed cases are more likely to be published, which may explain the very high proportion of grade ≥3 liver injury and may also influence the apparent outcomes of rechallenge. Second, data completeness varied substantially across reports. Exact age, time to onset, biochemical measurements, jaundice status, and follow-up information were not consistently available, resulting in different sample sizes across analyses. Third, laboratory measurements and definitions were heterogeneous across reports, and several variables required unit standardization. Fourth, the numbers of palbociclib- and dalpiciclib-associated cases were too small to permit meaningful comparative statistical analysis. In addition, not all included hepatic events represented the same pathophysiological phenotype. The single dalpiciclib case involved hepatitis B virus (HBV) reactivation leading to liver failure, while a small number of other reports involved distinct forms of hepatic injury, including pseudocirrhosis or vascular liver injury. These events may differ mechanistically from conventional idiosyncratic DILI. Their inclusion reflects the broader spectrum of clinically significant hepatic injury reported in association with CDK4/6 inhibitor therapy and should be considered when interpreting the pooled findings. Fifth, treatment decisions regarding corticosteroids, rechallenge, and switching were not randomized and were likely influenced by initial severity, cancer status, treatment response, clinician preference, and availability of alternative therapies. Finally, long-term oncological outcomes after discontinuation or switching were inconsistently reported.

Further studies should establish prospective multicentre registries of CDK4/6 inhibitor-associated DILI with standardized reporting of biochemical values, R ratio, causality assessment, histopathology, treatment, time to biochemical recovery, and long-term outcomes. Particular attention should be given to identifying predictors of recurrent DILI and determining whether switching between individual CDK4/6 inhibitors can be performed safely after severe hepatotoxicity. Such studies may help develop more individualized strategies that balance hepatotoxicity risk against the oncological benefit of continued CDK4/6 inhibition.

5. Conclusion

CDK4/6 inhibitor–associated DILI can be severe but was frequently reversible among reported cases. Recurrent DILI was substantially more frequently reported after same-drug rechallenge than after switching to an alternative CDK4/6 inhibitor. Switching after recovery may represent a potential strategy in selected patients. However, prospective studies are needed to better define its safety and feasibility and to identify optimal rechallenge approaches.

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