On the Occasion of the 80th Anniversary of the Faculty of Medicine of Charles University in Hradec Králové

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Last autumn we commemorated the 80th anniversary of the founding of the Faculty of Medicine of Charles University in Hradec Králové. A number of events were held and several publications were released, including a special issue of the *Časopis lékařů českých* entirely dedicated to this anniversary and to the faculty. At the ceremonial assembly of the academic community on 8 October 2025, the dean of the faculty, Professor Manďák, delivered an extensive speech in which he clearly described the historical circumstances of the faculty's foundation, its beginnings, development, and growth through various stages up to the present day.

Despite the many difficulties and changes related to both international and domestic political developments and the broader social climate over the past eight decades, the faculty has consistently fulfilled its main missions in student education, research, and scientific work. Outstanding physicians, teachers, and researchers have worked and continue to work here. Over the course of a demanding 80-year journey, the faculty has evolved into a modern educational and scientific research institution respected both nationally and internationally.

Throughout this development – one that was not always without challenges – an important role was played by the exceptionally supportive environment and conditions created by the authorities of the city of Hradec Králové and the entire East Bohemian region. Even before the faculty itself was established after the end of the Second World War, efforts had been made to build a regional university. The critical shortage of physicians after the war, together with the possibility of utilizing a well-functioning modern hospital staffed by many top specialists in Hradec Králové, were among the main reasons for choosing this city.

The excellent cooperation between the district hospital (later the University Hospital), the faculty, and the municipal and regional authorities has historically been one of the valuable attributes of mutual collaboration – something not entirely common elsewhere in the country. The spirit of interdisciplinary cooperation in Hradec Králové was further strengthened in 1969 with the establishment of the Faculty of Pharmacy of the university.

In this article we would also like to recall another unique and very important characteristic of the Hradec Králové Faculty of Medicine. Within the framework of interministerial cooperation, it prepares – as the only institution in former Czechoslovakia and now in the Czech Republic – prepares physicians for the needs of the Czech

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Armed Forces, within a joint study programme with the Military Medical Faculty of the University of Defence. This extremely significant and today highly relevant role represents a unique chapter and a distinctive feature in the faculty's history.

At the turn of the 1940s and 1950s, the international situation deteriorated with the emergence of two political-military blocs and the threat of a new conflict, potentially involving nuclear weapons. In order to ensure the country's defence capability, the armed forces expanded, but they faced a post-war shortage of professional military physicians. This situation created an objective need to establish an independent military medical university.

By Order of the President of the Republic No. 247, the Military Medical Academy (VLA) was established on 15 August 1951, and from 1955 it bore the name of Jan Evangelista Purkyně. After analysing several possibilities, Hradec Králové was selected – specifically its young medical faculty with its progressive orientation. The rapid establishment of the academy was possible only because it was built on the basis of the Faculty of Medicine of Charles University, including both its theoretical and clinical departments, which enjoyed an excellent reputation thanks to their staff. Most of these staff members became members of the academy. Among them were professors Baštecký, Hybášek, Janoušek, Krákora, Santholzer, Vanýsek, Vávra, Vavrda, and Vrtiš serving as officers in high ranks, as well as Bedrna, Blecha, Dvořák, Fingerland, and Lukl as civilian employees. These outstanding personalities became renowned representatives of their disciplines and contributed to the high quality of Hradec Králové and Czechoslovak medicine in education, clinical practice, and research. The Military Medical Academy, with its 40 departments and its own clinical hospital, became an educational and scientific centre and gained a strong reputation both domestically and internationally.

With the easing of international tensions and changes in domestic political conditions, further transformations in the status, organisation, and structure of this military medical institution followed. On 30 June 1958, the academy was dissolved and replaced by the Military Medical Research and Postgraduate Training Institute of J. E. Purkyně (VLVDÚ JEP). The Faculty of Medicine returned to civilian administration under the Ministry of Education as part of Charles University, and the clinical hospital was reintegrated into the civilian structure of the Ministry of Health. The main tasks of the VLVDÚ focused on research and postgraduate training and specialization of military physicians and pharmacists.

Under interministerial agreements, the undergraduate education of future military physicians continued at the restored civilian Faculty of Medicine of Charles University. Military students therefore complete the full curriculum of general medicine or dentistry, while additionally undergoing training in military-professional subjects, practical training in a vivarium or on simulators, and field exercises. In 1988, the institute was renamed again as the Military Medical Academy of J. E. Purkyně (VLA JEP).

Like the civilian Faculty of Medicine, the institution entered a completely new stage of development after November 1989. It underwent a transformation that significantly changed its military educational programmes, organisational structure, and staffing. With the establishment of the University of Defence of the Czech Republic, the school continued its activities from 1 September 2004 under the name Faculty of Military Health Sciences of the University of Defence (FVZ UO). On 1 January 2025, it was renamed once again to its current title: Military Medical Faculty of the University of Defence (VLF UO).

Today the Military Medical Faculty enters the third decade of its modern existence as a unique educational and scientific institution linking medicine, defence, and the state's security community. Its main mission is to prepare military and civilian healthcare professionals -physicians, dentists, pharmacists, and paramedics - capable of operating in a rapidly changing security environment, ranging from crisis situations and mass-casualty events to foreign missions, telemedicine, and modern threats associated with infectious diseases or hybrid conflicts. The faculty fulfils its mission through high-quality education, research, and professional expertise. Modern study programmes combine classical medicine with fields essential for military healthcare, including emergency medicine, epidemiology, toxicology, preventive medicine, radiation protection, and the specifics of field medical support. This enables the preparation of professionals capable of providing care not only in standard conditions but also in resource-limited, high-risk environments requiring rapid decision-making.

At the same time, the faculty plays a significant role in scientific research. Its departments focus systematically on infectious diseases, vaccinology, crisis management, military surgery, internal medicine, hygiene, toxicology, and radiobiology. The results of this work have practical impacts on both military and civilian healthcare systems, improving preparedness and contributing to innovations in prevention and health protection.

Today the significance of the faculty extends beyond the defence sector. Through its activities, it contributes to societal resilience, the development of professional knowledge, and the training of a new generation of physicians and healthcare professionals who combine professionalism, responsibility, and public service. Another future goal is to initiate the education and training of military nurses (general nursing). At a time when healthcare and security systems face growing challenges, the role of the Military Medical Faculty is clear: to be a stable pillar of expertise, a source of highly qualified professionals, and a guarantor that healthcare and health protection in both the armed forces and civilian sector will meet the needs of the present and the future.

Looking back at the 80-year history of the Faculty of Medicine of Charles University in Hradec Králové and the 75-year history of the Military Medical Faculty in Hradec Králové, it is evident how many things have changed and evolved in response to international political developments and the circumstances of the time. What can be stated with pride, however, is that the coexistence and close, mutually supportive cooperation between these two "sister" faculties has become beneficial and unique

example of mutually collaboration in medical education, science, and research.

The close integration of working teams, shared clinical workplaces, and joint activities in research and science – together with collegial and personal friendships often extending beyond formal interministerial agreements – runs like a red thread throughout the entire history of both institutions. This project linking a civilian and a military faculty is regarded as an exemplary model in military higher education, not only in the Czech Republic but also abroad.

Through the cooperation of both institutions, nearly three thousand military physicians and other military healthcare professionals have already been trained for the Czech Armed Forces. This long-standing collaboration between the ministries of education, health, and defence therefore contributes significantly to meeting the healthcare and defence needs of our country.

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Beyond the Algorithm: The ERC Guidelines 2025 and the Maturity of Resuscitation Medicine

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The European Resuscitation Council Guidelines 2025, officially launched as the Guidelines on Cardiopulmonary Resuscitation 2025 on 22 October 2025 in Rotterdam and published in *Resuscitation* (1) as a thematic collection of guideline papers, represent far more than a scheduled update of resuscitation algorithms. That reading would be too narrow. The ERC Guidelines 2025 are better understood as a portrait of a discipline that has entered a new phase in its understanding of the continuum of resuscitation care. In these guidelines, resuscitation medicine is not reduced to the dramatic moment of cardiac arrest. It is presented as a continuum of knowledge, decision-making, technical skill, system organization, ethical responsibility, and long-term outcome. The algorithm retains its grammar, but not the whole language of care.

This is what makes the 2025 guidelines important. They document the transformation of resuscitation from an acute technical intervention into a mature clinical discipline situated at the intersection of time, pathophysiology, teamwork, system design, and value-based decision-making. Resuscitation remains inseparable from urgency, but contemporary resuscitation medicine shows that speed without structure, technical correctness without a functioning system, and intensity of treatment without an ethical frame are not enough. Saving life in a critical moment requires not only hands capable of performing the correct intervention, but also an environment in which that intervention can be delivered early, reliably, in the appropriate clinical context, and with a clear pathway to subsequent care.

This shift from algorithm to system is visible throughout the guidelines. Resuscitation is no longer merely a question of what happens in the minutes after collapse. It is shaped by how the system works before cardiac arrest, during cardiac arrest, and after return of spontaneous circulation. Recognition of deterioration, activation of help,

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first aid, basic life support, automated external defibrillation, dispatcher assistance, emergency medical service organization, in-hospital rapid response systems, advanced life support, post-resuscitation care, registries, and audit all form a single clinical and organizational continuum. The chain of survival is therefore not only an educational metaphor. It is an operational responsibility. Survival after cardiac arrest is not the property of an isolated intervention; it is a property of the system.

The concept of systems saving lives is consequently one of the central messages of the ERC Guidelines 2025. There is no isolated hero in resuscitation detached from the system. Citizens, dispatchers, first responders, ambulance crews, emergency departments, catheterization laboratories, intensive care units, rehabilitation professionals, and registries are all part of the same trajectory of care. Each enters at a different point, with different competencies, but in relation to the same outcome. Where one link is absent or weak, even an otherwise excellent intervention loses part of its effect. In resuscitation, a system weakness rapidly becomes a biological loss.

The technical core of resuscitation has not lost its importance. Quite the opposite. High-quality chest compressions, early defibrillation, adequate ventilation, treatment of reversible causes, and well-conducted advanced life support remain decisive interventions. Their strength lies in simplicity, reproducibility, and clarity. This is precisely why algorithms are indispensable: under cognitive overload, time pressure, and complex team dynamics, they reduce chaos, create a common language, and give rhythm to decision-making. Yet the ERC Guidelines 2025 also remind us that a correct algorithm does not absolve clinicians from thinking. Special circumstances of cardiac arrest demonstrate that standardization and individualization are not opposites. Cardiac arrest is not a diagnosis, but the final common pathway of many pathophysiological processes. Successful resuscitation must therefore be more than a response to the rhythm on the monitor; it must be a response to the cause, the context, and the possibility of meaningful causal intervention.

The integration of ethics into the core of resuscitation medicine is another sign of maturity. Decisions to start, continue, or terminate resuscitation are not merely technical judgments about the probability of return of spontaneous circulation. They are clinical decisions framed by patient values, goals of care, proportionality, and previously expressed preferences. Advance care planning, DNACPR decisions, family presence, termination of futile resuscitation, and organ donation are not peripheral subjects that appear after medicine has done its work. They are part of medicine itself. A discipline capable of rapid and aggressive action must be equally capable of determining when such action is meaningful, proportionate, and aligned with what good care would mean for this particular patient.

The significance of the ERC Guidelines 2025 also depends on epidemiology, registries, and outcome measurement. Resuscitation medicine must know itself. It must know how many cardiac arrests occur out of hospital and in hospital, who initiates resuscitation, how often an AED is used, how rapidly the system responds, how many patients survive, and in what neurological condition. Without data, quality becomes impression. Registries, audit, and standardized reporting are not administrative ornaments attached to clinical work; they are prerequisites for responsible improvement. Only a measured system can identify its weaknesses, compare itself with others, and move from conviction to quality.

Between scientific recommendation and patient survival lies another decisive space: education and implementation. Guidelines do not become a clinical reality because they are published. They become clinical reality when they are translated into teaching, simulation, team training, feedback, debriefing, local protocols, and the everyday culture of practice. In resuscitation, knowledge without rehearsal quickly becomes uncertainty, and rehearsal without measurement becomes ritual. Simulation is not merely an imitation of reality for educational purposes; it is a safe space in which clinical reality can be processed before it occurs in a real patient. Team culture does not arise at the moment of cardiac arrest. It must be built before it.

The breadth of the ERC Guidelines 2025 further reminds us that resuscitation medicine is not one physiological world. Newborns at the threshold between intrauterine and extrauterine life, children threatened by hypoxia or shock, adults with cardiac arrest in the community, frail in-hospital patients with previously expressed treatment limitations, and survivors after return of spontaneous circulation all require different forms of reasoning. A unifying principle exists, but its clinical expression changes with age, cause, setting, prognosis, and available resources.

One of the key shifts reinforced by the ERC Guidelines 2025 is that return of spontaneous circulation is not the end of resuscitation. It is a threshold event after which another, often more complex, phase of care begins. Diagnosis of the cause of arrest, oxygenation, ventilation, haemodynamic stability, coronary reperfusion, seizure control, temperature management, neurological prognostication, rehabilitation, psychological consequences, and quality of life determine whether biological survival becomes a return to life. Survival to intensive care admission, survival to hospital discharge, and long-term neurological outcome are not interchangeable endpoints. Post-resuscitation care is therefore not an epilogue. It is an integral part of resuscitation, where the true value of acute success is determined.

The ERC Guidelines 2025 are therefore not simply a document on how to resuscitate. They are a document on how resuscitation care should be conceived, organized, taught, measured, and ethically grounded. Their greatest challenge begins not at publication, but at implementation. Their significance will be defined by what hospitals, emergency medical services, educators, professional societies, registries, and clinical teams are able to make of them. The value of guidelines is ultimately measured not by their publication but by the people, teams, and systems that transform them into timely, competent, ethical, and measurable care.

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Middle Meningeal Artery Embolization (MMAE) Versus Surgical Evacuation for Recurrent and Refractory Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Recurrent and refractory chronic subdural hematoma (cSDH) remains a significant neurosurgical challenge due to high recurrence rates and morbidity associated with repeated surgical interventions. Middle meningeal artery embolization (MMAE) has recently emerged as a minimally invasive alternative, but its efficacy compared to surgical evacuation in this specific subgroup has not been systematically evaluated.
Methodology: A systematic search of Pubmed was conducted to identify studies reporting outcomes of MMAE and surgical evacuation in recurrent or refractory cSDH cases. Pooled efficacy rates and complication rates were extracted and analyzed using fixed-effects meta-analysis. Statistical significance was assessed with a p-value threshold of 0.05.
Results: Sixteen studies were included in the meta-analysis. 181 patients underwent surgical evacuation while 97 patients underwent MMAE for recurrent and refractory cSDH. MMAE demonstrated significantly higher efficacy with a pooled success rate of 95% versus 84% for surgery (p=0.002, I2=0). Complication rates were lower in the MMAE group (6%) versus the surgical group (10%), though the difference was not statistically significant (p=0.06, I2=0).
Conclusions: MMAE shows promise as a highly effective and safe treatment modality for recurrent and refractory cSDH, potentially surpassing surgical evacuation in both efficacy and safety. Given these findings, MMAE should be strongly considered not only as a salvage therapy but also as a frontline treatment option in this challenging patient population. Further high-quality randomized controlled trials are warranted to confirm these results and refine patient selection criteria.

KEYWORDS

Middle meningeal artery embolization; recurrent; refractory; chronic subdural hematoma; surgery

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INTRODUCTION

Chronic subdural hematoma (cSDH) is a common neurosurgical condition, especially in the elderly, typically caused by minor head trauma and characterized by the slow accumulation of blood between the dura and arachnoid membranes (1). Surgical evacuation via burr-hole craniostomy is the standard treatment; however, recurrence occurs in up to 30% of cases, often requiring repeat interventions and prolonged care (2).

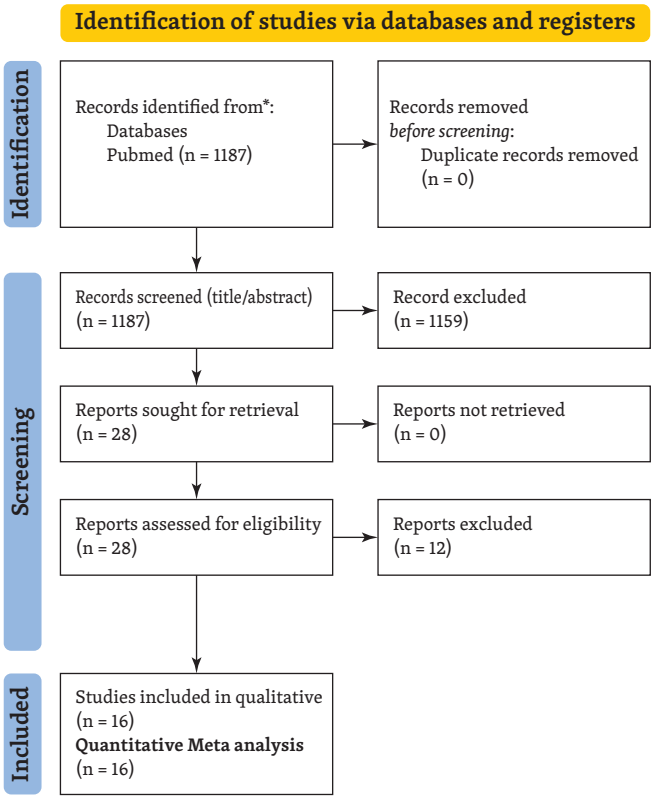
Middle meningeal artery embolization (MMAE) has recently emerged as a minimally invasive alternative or adjunct, aimed at occluding the vascular supply to the neo membranes that contribute to hematoma recurrence (3). Several studies have demonstrated promising outcomes with MMAE, particularly in reducing recurrence rates compared to surgical evacuation (4). While comparative studies and meta-analyses have examined MMAE versus surgery for cSDH in general (5), there is a lack of comprehensive reviews specifically focused on recurrent and refractory cases, a challenging subset with no clearly established management algorithm.

This systematic review and meta-analysis aims to bridge this gap by systematically evaluating the evidence comparing MMAE and surgical evacuation specifically in the context of recurrent and refractory chronic subdural hematomas, with a focus on clinical outcomes, recurrence, and safety profiles.

METHODS

LITERATURE SEARCH

We screened PubMed systematically as per the PRISMA guidelines (Fig. 1) from inception till May 1, 2025 for articles reporting the outcomes in patients undergoing surgery or MMAE for recurrent and refractory cSDH. Search strategy was generated using the terms similar to and including "MMAE", "surgery", "recurrent cSDH" and "refractory cSDH" along with boolean operators, AND, OR, NOT. The reference lists of the respective articles were also screened manually to prevent exclusion of any potential study.



INCLUSION AND EXCLUSION CRITERIA

We included the studies that were, 1) Reported in English language, 2) included patients with recurrent and refractory cSDH, 3) underwent surgery or MMAE, 4) had adequate outcomes data, success rate, and complications rate. Studies were excluded if they, 1) Were in a non-English language, 2) Had mixed data for recurrent and primary cSDH, 3) had inadequate outcomes data, 4) were reviews, case reports, editorials or commentaries. Two authors (BP, NP) independently reviewed the articles as per the inclusion and exclusion criteria and collected the required data for analysis. The senior author (IB) settled any disagreements.

In this review, 'recurrent' cSDH was defined as the re-accumulation of hematoma requiring intervention within 6 months of initial surgical evacuation. 'Refractory' cSDH was defined as persistent or re-accumulating hematoma that failed to resolve despite conservative treatment or more prior procedural interventions.

DATA COLLECTION

Following data points were extracted from each study included in this analysis:

- Patient's details (number of patients, age, gender)
- cSDH characteristics (volume)
- Type of therapy: Surgery or MMAE
- Follow up
- Outcomes – success rates and complication rates

QUALITY ASSESSMENT

Newcastle-Ottawa Quality Assessment Scale was utilized to assess the level of evidence of each study

STATISTICAL ANALYSIS

Meta-analysis was conducted using Jamovi software (version 2.3.1). DerSimonian and Laird models were generated to compare success rates and complication rates of surgery and MMAE.

RESULTS

Following PRISMA, 1187 studies were retrieved for title and abstract search. Twenty eight studies were selected for full article retrieval and finally, 16 studies met the inclusion and exclusion criteria. A total of 16 articles were included in this review. Nine studies reported the utilization of MMAE (Table 1), while seven studies involved invasive surgical procedures (Table 2).

Tab. 1 Summary of studies reported on MMAE for recurrent and refractory cSDH.

Author, year	Type of embolus	N	Age (years)	Gender	Volume (ml)/ thickness (mm)	Successful (%)	LOS (days, SD)	Complications	Quality of study
Liebert et al., 2023[6]	17 Onyx, 5 Squid & 1 PHIL	23	78.3	–	75.1 ml	20 (87)	5.45 (1.97)	2	7 Good
Dofuku et al., 2022[7]	NBCA	9	85	6M 3F	30 mm	9 (100)	–	0	8 Good
Tempaku et al., 2015[8]	PVA	5	83	4M 1F	–	5 (100)	–	0	7 Good
Link et al., 2018[9]	PVA	6	64.5	5M 1F	12.57 ml	6 (100)	–	0	8 Good
Nakagawa et al., 2019[10]	NBCA	20	78.3	14M 6F	–	20 (100)	–	0	7 Good
Mino et al., 2010[11]	Gelatin sponge & Guglielmi detachable coils	4	73	4M 0F	–	4 (100)	–	0	7 Good
Hashimoto et al., 2013[12]	5 NBCA, 1 PVA	5	71.4	3M 2F	–	5 (100)	–	0	7 Good
Kim, 2017[13]	PVA	20	73.65	14M 6F	19 mm	19 (95)	19.96 (13.44)	5	8 Good
Matsumoto et al., 2018[14]	NBCA	5	68.2	5M 0F	–	5 (100)	–	–	8 Good

n-butyl cyanoacrylate (NBCA), polyvinyl alcohol (PVA)

Tab. 2 Summary of studies reported on Surgical evacuation for recurrent and refractory cSDH.

Author, year	Modality	Demographics of patients	cSDH characteristics	Successful (%)	Complications	Quality
Liebert et al., 2023[6]	Surgery	27 hematomas 24 patients mean age:78.3 yrs	75.1ml volume, 2.67mm midline shift	19 (70.3)	2 patients developed a subdural empyema	7 Good
Kim 2017[13]	Surgery	24 hematomas 23 patients. Mean age: 65.65 yrs 16M, 7F	21mm thickness	16 (67.7) Hospital stay: 14.25 days	4	8 Good
Matsumoto et al., 2018[14]	Craniotomy	n=2 Mean age: 70yrs 2M	Refractory Organised: 2	2 (100)	0	8 Good
	Irrigation and drainage (I & D)	n=7 Mean age: 75yrs 6M, 1F	Refractory Organized: 0	7 (100) 1 patient underwent I & D 4 times	0	
Ichimura et al., 2020[15]	Neuroendoscope + small craniotomy	n=17 Mean age:83yrs 13M, 4F	Max diameter: 22.4 mm (range 15-37mm) Septations: 10	16 (94.1)	4 (postoperative seizures)	8 Good
Santarius et al., 2010[16]	Burr Hole without drain	n=36 Mean age:73 yrs 25M, 11F	-	24 (67)	6 1 subdural empyema, 3 pneumonia, 1 ASDH, 1 brain swelling.	8 Good
	Burr Hole with drain	n=14 Mean age:78 yrs 11M, 3F		12 (86)	2 1 ASDH, 1 subdural empyema	

Author, year	Modality	Demographics of patients	cSDH characteristics	Successful (%)	Complications	Quality
	Burr hole with subdural-to-peritoneal catheter	n=13 Mean age:79 yrs 9M, 4F		12 (92)	1 brain swelling	
Yamamoto et al., 2023[17]	Butterfly needle tap and suction	34 hematomas 26 patients Mean age: 78.8 yrs 19M, 7F	Midline shift: 7.5mm 42ml mean volume	21 (81)	2 headaches	8 Good
Sato et al., 2001[18]	Ommaya reservoir	23 hematomas, 16 patients Mean age: 74 yrs 13M, 3F	Mean volume: 100ml 11 unilateral 6 bilateral	13 (81.25) The hematoma size decreased to <3 mm at a median of 60 days after introduction of the reservoir	Occlusion of reservoir in 2 Minor bleeding in 2	8 Good

Ninety seven patients were treated with MMAE for their recurrent and refractory cSDH at a mean age of 75 years (SD: 6.7 years) with predominant male population (n=55, 74%). The most commonly used embolic agent was n-butyl cyanoacrylate (NBCA) (39 patients) followed by polyvinyl alcohol (PVA) (32 patients) and Onyx (17 patients).
Two hundred thirteen hematomas in 181 patients were treated with surgical evacuation. The mean age was 75.5 years (SD: 5 years) with 114 males (74%) and 40 females. There was no significant difference in the mean age (p=0.87) or gender wise distribution (p=0.96) between the MMAE and surgery cohorts.
There was a significant difference in the success (95% vs 84%, p=0.003, Welch's test, respectively) and complication rates (6% vs 10%, p=0.038, Mann Whitney test, respectively) between MMAE and surgical groups.
Fig. 2 depicts the longitudinal trends in the management options for recurrent and refractory cSDH.

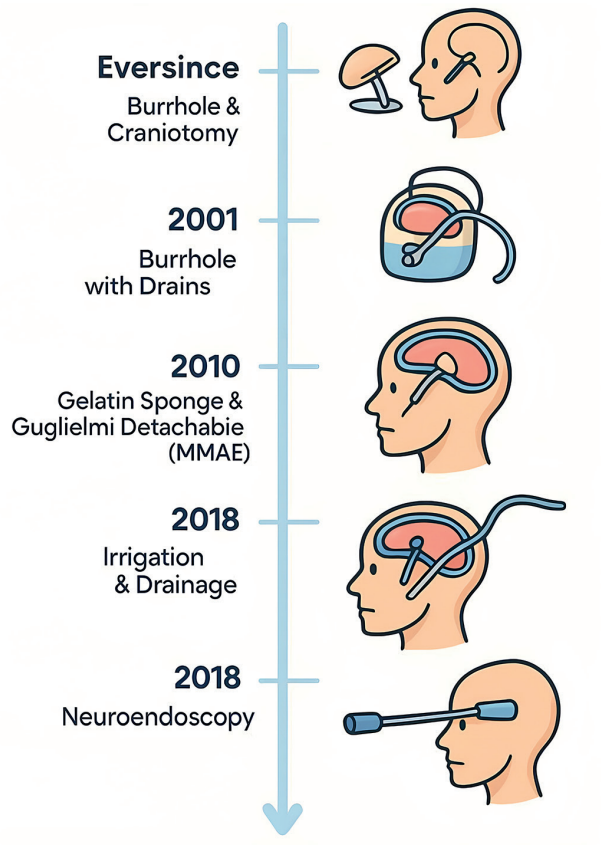


Fig. 2 Longitudinal trends in the management options for recurrent and refractory cSDH.

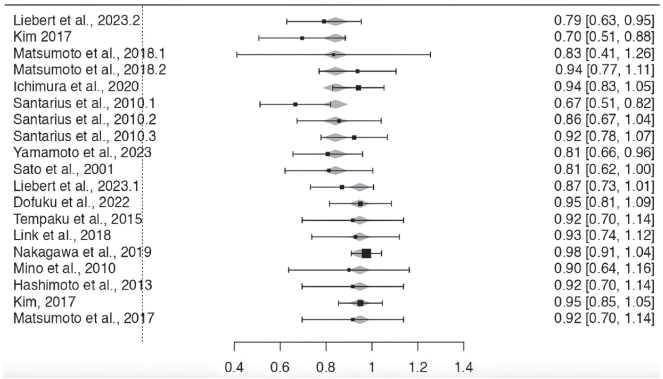


Fig. 3 Meta analysis of Success rates of MMAE and surgery for recurrent and refractory cSDH.

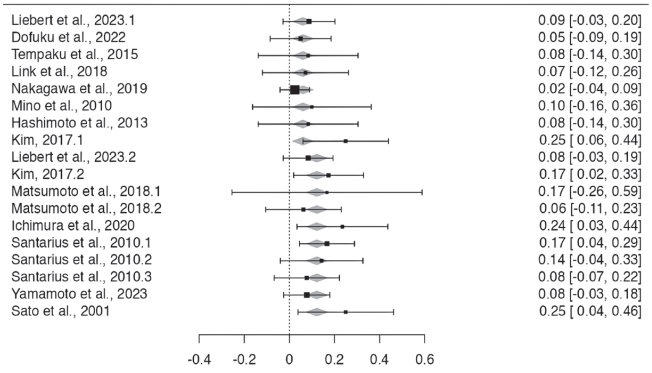


Fig. 4 Meta analysis of Complication rates of MMAE and surgery for recurrent and refractory cSDH.

META-ANALYSIS

The pooled success rate of MMAE was significantly higher than the surgery group (95% vs 84%, I^2=0%, p=0.002) (Fig. 3). However, there was no significant difference in the pooled complication rates of both groups (6% vs 10%, respectively I^2=0%, p=0.06) (Fig. 4).

DISCUSSION

This meta-analysis demonstrates that MMAE offers significantly higher efficacy than repeat surgical evacuation in the management of recurrent and refractory cSDH, with pooled success rates of 95% versus 84%, respectively

(p=0.002). To our knowledge, this is the first comprehensive meta-analysis specifically comparing MMAE and surgical evacuation in the challenging subgroup of recurrent and refractory cSDH patients, filling an important gap in the literature. These findings provide compelling evidence that MMAE is not only a viable alternative but may be a superior therapeutic option across a broad spectrum of patients. By targeting the vascular supply to the hematoma's outer membrane, MMAE addresses the pathophysiological driver of recurrence, chronic inflammation and fragile neovascularization; rather than merely removing the hematoma volume (18). This mechanistic advantage likely underpins the higher efficacy seen in this analysis and positions MMAE as a potentially transformative strategy in the treatment algorithm for recurrent cSDH.[5] Moreover, while the difference in complication rates between MMAE (6%) and surgical evacuation (10%) was not statistically significant (p=0.06), the trend favors MMAE in terms of safety. Reported complications with MMAE were infrequent, mostly minor, and often self-limiting, including groin hematomas and transient neurological symptoms. Surgical evacuation, in contrast, carried higher risks of infection, acute rebleeding, and postoperative seizures, particularly in older or medically fragile patients. Given its minimally invasive nature, superior efficacy and favorable safety and efficacy profile, MMAE shows promise not only as a salvage option but as a potential first-line treatment for recurrent – and possibly even primary – cases of cSDH in the future. Though the majority of the studies reported the use of MMAE in recurrent CSDH, the study by Hashimoto et al. implicated the utilization of MMAE in refractory cases (12). Similarly, only one study by Matsumoto et al. reported the surgical management of refractory cases (14). Therefore, there is a dearth of literature in the management of refractory cSDH and warrants more research.

MIDDLE MENINGEAL ARTERY EMBOLIZATION (MMAE)

MMAE has emerged as a successful and efficacious management option for recurrent and refractory cSDH with an estimated efficacy of 95% on this study. Of the nine studies included in this analysis, one study each reported a success rate of 87% and 95%, while the other seven had a success rate of 100%, establishing the superiority of MMAE to other techniques. Liebert et al (6) described that MMAE is suited for recurrent hematomas with a lower pre interventional volume and midline shift as well as mildly symptomatic cases.

In their comparative study between surgery and MMAE for recurrent cSDH, MMAE had significantly higher efficacy than surgery (87% vs 70.3%), shorter length of hospital stay and superior ability to detect treatment failure earlier. In another comparative study by Kim et al. (13) the second recurrence rates were significantly lower in the MMAE group as compared to the surgical group (3.8% vs 33.3%, p=0.024). Furthermore, MMAE significantly decreased the time required to restore the bihemispheric symmetry of the brain (34.65 vs. 98.29 days; $P < 0.001$). Owing to the lower rates of recurrence for MMAE, MMAE may be performed prophylactically in patients with the risk factors for recurrence after burr hole especially in elderly patients on anticoagulant therapy. Dofuku et al. (7) established a time frame appropriate for ensuring a good outcome. MMAE was performed within 2 weeks of the second burr hole surgery at a median duration of 10 days and gave a 100% success rate. They embolized both the anterior and posterior branches of MMA, irrespective of the dominant branch and found no recurrence or need of surgical rescue. However, the anatomical variations in the branches need to be kept in mind since that could give rise to complications, for instance, the anastomosis of the anterior branch with the ophthalmic artery, which can be catastrophic.

The most commonly used embolic agent was NBCA (39 patients) followed by PVA (32 patients) and Onyx (17 patients). NBCA is a liquid adhesive with a rapid onset of action, decreasing the operation time and facilitates performing the procedure under local anesthesia, which is desirable in elderly patients. NBCA and Onyx do not let the catheter tip adhere to the vessel wall, allowing for a long duration administration. Additionally, these can be easily visualised on CT, which is of importance since the agent has the tendency to penetrate the inner and outer membranes of the hematomas. PVA has an advantage of being cost effective and reaching a wider anatomical vasculature over NBCA and onyx which provides 'stump' embolization proximally, owing to the ability of the PVA particles to travel more distally within the MMA and restricting the formation of newer distal collaterals. The major disadvantage of onyx is that it is DMSO based with a higher risk of cranial nerve injury and toxicity.

The pooled complication rate for the MMAE cohort was 6% (n=7), however none of the patients had any permanent neurological deficits and recovered rapidly in the follow up period. MMAE is usually performed after gaining access to the MMA via the radial or femoral artery route. A novel route to perform MMAE through a puncture directly in superficial temporal artery in a patient with aortic dissection involving common carotid artery precluding the access through radial or femoral artery is described by Eccles et al. (19). This significantly reduces the operative time, however best performed at the hands of a trained personnel.

INSIGHTS FROM RECENT RANDOMIZED TRIALS

The landscape of cSDH management experienced a paradigm shift in 2024 with the publication of three landmark multicenter randomized controlled trials: MAGIC-MT, EMBOLISE, and STEM (29-31). While our meta-analysis highlights the efficacy of MMAE in the recurrent and refractory population, these recent trials provide robust, high-level evidence regarding its timing and application; specifically delineating its role as an adjunctive measure versus a standalone, first-line therapy.

As an adjunctive treatment to surgery, MMAE has definitively proven its value in preventing recurrence. Both the EMBOLISE and STEM trials evaluated MMAE performed concurrently with or shortly after surgical evacuation. In the EMBOLISE trial, patients who received adjunctive Onyx embolization after surgery had a significantly lower rate of

hematoma recurrence requiring reoperation compared to those who underwent surgery alone (4.1% vs. 11.3%). Similarly, the STEM trial demonstrated a significant reduction in treatment failure and recurrence when embolization was used alongside standard surgical care. By shutting down the fragile neovasculature of the dural membrane, adjunctive MMAE acts as a prophylactic mechanism, strongly supporting its routine use following initial evacuation to prevent patients from entering the refractory cycle.

Furthermore, recent data increasingly supports MMAE as a first-line, standalone treatment for appropriately selected patients, potentially bypassing the need for surgery altogether. In the MAGIC-MT trial, symptomatic patients randomized to receive standalone MMAE alongside conservative management showed significantly lower rates of subsequent surgical intervention and disease progression compared to those receiving conservative management alone. For patients with recurrent or refractory cSDH who have already failed standard surgical evacuation, these findings are particularly highly relevant. They suggest that standalone MMAE can successfully halt the inflammatory cycle of rebleeding without the morbidity of repeat open surgery. Consequently, rather than viewing MMAE solely as a salvage option after multiple surgical failures, the convergence of this recent RCT data suggests MMAE should be strongly considered as a primary, upfront intervention for early recurrences, or as a standalone first-line option for medically fragile patients with non-life-threatening hematoma volumes.

SURGICAL INTERVENTION

In the past decades, burr hole was the mainstay treatment for recurrent and refractory cases, due to the absence of any other efficacious alternatives. However, the success rates were moderate and recurrence rates were high, necessitating innovations in already existing modalities at the time, which included the use of Ommaya reservoirs and drains. Burr hole with external drain and subdural to peritoneal catheter had significantly higher success rates (86% vs 67%, 92% vs 67% respectively) and lower complication rates than burr hole alone for recurrent cSDH (16). Ommaya reservoirs placed between the scalp and the skull are proven to be instrumental in managing refractory cases complicated by severe diseases with a success rate of 81.25%. Matsumoto et al. (18) achieved a success rate of 100% for their patients with refractory cSDH undergoing craniotomy and I&D (14). They suggested MMAE to be suitable for refractory cases without organised hematomas, while for organized hematomas large craniotomy or mini craniotomy be performed as per the size and location of hematoma with a 100% success rate (14). The use of a rigid neuroendoscopy was implicated for the first time for recurrent cSDH by Ichimura et al. in 2020 in 17 patients (15). They performed a minicraniotomy at the same site as previous surgery followed by entry of the endoscope and the suction tube to evacuate the hematoma and remove the septations. Thereafter, the inner membrane was incised allowing for brain expansion. The endoscope facilitated the easy visualisation of the hematoma and the septations making the evacuation an unchallenging task. Only one patient underwent endoscopic evacuation twice owing to the regrowth of hematoma. Four patients had postoperative seizures which was easily managed with one time administration of antiepileptics in the hospital. Endoscopic evacuation not only managed but also reduced the recurrence of cSDH (15). In a study of 229 cases divided into two cohorts, endoscopic membranectomy and non endoscopic evacuation of cSD, the recurrence rate in the endoscopic group was 0% and significantly lower than the second cohort (20).

Yamamoto et al. introduced a novel and innovative technique, Butterfly needle tap and suction (BTS) for recurrent cSDH wherein hematoma was punctured percutaneously with a butterfly needle (NIPRO Safe Touch PSV, 23G × 3/4, 0.6 × 19 mm) at the site of previous burr hole connected to a 20 ml syringe and evacuated at a speed of 5 ml/min (17). The mean number of punctures was 2.2 and only 5 patients (19%) in their cohort needed a reoperation. BTS can be performed bedside, provided the hemorrhagic complications are prophylactically managed. This can be achieved by opening the dura in a cruciate manner and cauterising the critical vessels until occlusion, implicated in the burr hole during first surgery. Periprocedural headache was observed in 2 patients, which could be attributed to the temporary decrease in the intracranial pressure while aspirating the hematoma, giving rise to intracranial complications. Therefore, aspiration must be performed slowly at a speed of ≤ 5 ml/min (17).

In a refractory case with recurrence over 5 times, fibrin glue injection into the hematoma cavity after fifth surgery achieved full resolution of cSDH (21). 5 ml of 10,000 U Urokinase for two days directly injected into the hematoma cavity achieved a rapid and long term resolution of a bilateral refractory cSDH without any residual neurological deficits (22). Although the volume of hematoma was less than 50 ml in both these case reports, minimally invasive nature, zero complications and faster recovery makes fibrin glue and urokinase promising modalities.

ROLE OF MEDICATIONS

One study described the efficacy of pharmacological agents in the management of recurrent cSDH. Dexamethasone achieved a success rate of 71% and baseline functional rate of 87.5% in recurrent cSDH patients who took 4mg oral or systemic dexamethasone every 8 hours for 3 days.23 When compared with the cohort that underwent surgical evacuation of recurrent cSDH, there was no significant difference in the outcomes. Complication rate was 12.5%; complications were transient and easily managed within a month. A recent study on Japanese herbal medicines established their role in decreasing the recurrence of cSDH (24-28). The cohort of patients receiving the japanese herbal extracts had significantly lower recurrence rates than the control group undergoing surgery alone. The complication rates were 0%.

LIMITATIONS

The majority of the studies included for MMAE in the meta-analysis are from the developed world, limiting the understanding of its efficacy since the burden of

neurotrauma is highest in the developing world. Secondly, there is scarcity of studies in refractory cSDH and warrants more research to derive meaningful conclusions. Third, we could not assess other measures like operative time, blood loss and length of hospital stay in the meta analysis owing to the inadequacy of data. Fourth, there is a relative paucity of randomized controlled trials directly comparing MMAE and surgery, limiting the strength of causal inferences. Lastly, long-term functional outcomes and quality-of-life measures were inconsistently reported, restricting assessment of the broader clinical impact.

CONCLUSION

With the advancement in the understanding of recurrent cSDH, the shift of management has happened from surgical evacuation to MMAE. MMAE is a promising approach to manage recurrent and refractory cSDH cases with a pooled efficacy of 95% and minimal complications across all age groups. However, more complicated refractory cases might require surgical intervention and direct injections into the hematoma cavity.

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The Emerging Role and Clinical Impact of Vitamin D Supplementation in Breast Cancer Patients Undergoing Chemotherapy: A Systematic Review

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ABSTRACT

Introduction: Breast cancer is the most common cancer in women and is often diagnosed at an advanced stage. Chemotherapy plays a crucial role in disease control but is limited by toxicity and response variability. Vitamin D, with its biological functions and the high prevalence of deficiency in patients, has potential as an adjuvant therapy to improve treatment response and clinical outcomes.
Objective: To integrate existing evidence on the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy, focusing on its impact on treatment response and clinical outcomes.
Methods: This systematic review followed PRISMA guidelines and included RCTs, cohort, and case-control studies evaluating vitamin D supplementation in adult women with breast cancer undergoing chemotherapy. A comprehensive search across five databases up to June 2025 was conducted, applying the pre-established PICOS criteria, with filtering, data extraction, and quality assessment performed. This systematic review has been prospectively registered in the PROSPERO database (CRD420251142938).
Results: This systematic review identified six eligible studies involving breast cancer patients undergoing chemotherapy, with interventions ranging from low- to high-dose vitamin D, either alone or in combination with synbiotics. Vitamin D supplementation in breast cancer patients undergoing chemotherapy has been associated with improved clinical outcomes, including enhanced nutritional status, reduced inflammatory and cardiotoxic biomarkers, and increased pathological complete response (pCR) and disease-free survival (DFS).
Conclusion: Vitamin D supplementation during chemotherapy shows potential benefits in breast cancer patients, but large-scale standardized trials with long-term follow-up are needed to confirm its impact on survival outcomes.

KEYWORDS

breast cancer; chemotherapy; clinical outcomes; vitamin D supplementation

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INTRODUCTION

Breast cancer is a global health problem with the highest incidence among women in various countries. According to WHO data from 2022, there were approximately 2.3 million new cases and 670,000 deaths from breast cancer worldwide. The prognosis of this disease is strongly influenced by the Human Development Index (HDI), where five-year survival rates can reach over 90% in countries with a high HDI, while in countries with a low HDI, the rate is much lower. Mortality trends show a decline in 29 countries with a very high HDI, and seven of these, including Belgium and Denmark, have achieved the Global Breast Cancer Initiative target of an annual decline of at least 2.5%. Conversely, in about half of the countries monitored, mortality rates are increasing by 1–5% per year. Projections for 2050 predict a significant increase in the burden of this disease, with new cases increasing by 38% and deaths by 68%, which will disproportionately impact countries with a low HDI (1, 2). In Indonesia and Southeast Asia, although data vary, there is a tendency for breast cancer to be diagnosed at an advanced stage due to differences in access to screening and treatment services, which impacts clinical outcomes, with approximately 64.5% of breast cancer cases being diagnosed at stage III or IV (3). Barriers, such as limited early detection facilities, such as mammography, low public awareness, socioeconomic factors, and inadequate health infrastructure, also exacerbate delays in diagnosis and case management (3–5).

Breast cancer management is generally multimodal, including surgery, radiotherapy, hormone therapy, targeted therapy, and chemotherapy, depending on the stage and characteristics of the tumor. Chemotherapy plays a crucial role in breast cancer treatment because it can control micrometastases and improve survival rates, especially in aggressive subtypes, through primary neoadjuvant, adjuvant, and palliative strategies. Neoadjuvant chemotherapy is administered before surgery to shrink the tumor, permitting conservative management and assessing response to therapy. In locally advanced or inoperable cases, this strategy can result in a pathological complete response (pCR), which is associated with improved overall survival (OS) and disease-free survival (DFS) (6, 7). Postoperative adjuvant chemotherapy aims to eliminate residual microscopic cancer cells, reduce the risk of recurrence, and improve prognosis (8, 9). In metastatic cancer, palliative chemotherapy is used to reduce symptoms, slow progression, and improve quality of life, with a median OS of approximately two years. Monotherapy is often chosen to suppress toxicity, while continued administration until progression remains effective without compromising quality of life (10). However, excessive use in low-risk patients raises concerns about overtreatment, requiring an individualized approach based on tumor characteristics (7).

Chemotherapy remains a key component of breast cancer management, but its use faces significant challenges due to toxicity and interpatient response variability. Side effects such as nausea, alopecia, peripheral neuropathy, and organ dysfunction have been reported to seriously impact quality of life, with severe hematologic toxicity occurring in 38.6% of patients and gastrointestinal toxicity in 12.9%, in addition to psychological burdens that reduce well-being (11, 12). Response variability is influenced by tumor characteristics, such as triple-negative subtypes that are more susceptible to toxicity, and genetic factors such as polymorphisms in drug metabolism and DNA repair genes that can exacerbate side effects. In addition to patient factors such as age, nutritional status, and comorbidities, patient factors such as age, nutritional status, and comorbidities (11, 13). This situation results in treatment outcomes that are not always optimal for all patients, so a personalized therapy approach and patient-based outcome reporting are considered essential to increase effectiveness while minimizing side effects (13).

Vitamin D, particularly its active form 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], has biological functions beyond calcium-phosphate regulation by inhibiting proliferation, promoting differentiation, inducing apoptosis, and modulating inflammation and immune responses through the vitamin D receptor (VDR). These activities are associated with anticancer properties, including increased cytotoxicity against tumor cells, enhanced immunity, and suppression of inflammatory processes that contribute to cancer progression (14–16). The VDR receptor expressed on immune cells also contributes to a more effective antitumor response. In a clinical context, over 70% of breast cancer patients are reported to have vitamin D deficiency, which is associated with a poor prognosis and a higher risk of recurrence (17). While higher vitamin D levels are associated with improved survival outcomes, evidence regarding the association between VDR expression and mortality remains inconsistent (18).

Previous studies have shown that breast cancer patients often have very low vitamin D levels. An observational study in Yogyakarta reported an average vitamin D level of around 8.80 ng/mL before chemotherapy, with more than 80% of patients categorized as severely deficient, and this level tended to decrease after therapy (19). A recent randomized clinical trial showed that vitamin D supplementation can improve pathological complete response (pCR) in breast cancer patients undergoing neoadjuvant chemotherapy, with both cholecalciferol 2,000 IU/day for six months and vitamin D3 50,000 IU/week increasing the chance of achieving pCR compared to the control group (20, 21). This evidence supports the potential of vitamin D as an adjuvant therapy to improve treatment response while maintaining nutritional status and reducing inflammation.

However, research results remain variable due to variations in dosage, duration of supplementation, patient characteristics, and outcome parameters studied. A knowledge gap remains regarding the effect of vitamin D supplementation on patient clinical outcomes. Given that chemotherapy, while effective in improving survival, is often limited by toxicity, immunosuppression, and response variability that reduce therapeutic efficacy, adjuvant strategies such as vitamin D supplementation are becoming increasingly important. Therefore, a systematic review is needed to integrate the available evidence regarding the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy.

METHODS

STUDY DESIGN AND SETTING

This study was designed as a systematic review and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to summarize and evaluate the available evidence on the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy, with particular emphasis on its impact on clinical outcomes.

SEARCH STRATEGY

A systematic literature search was carried out across five major databases: PubMed, ScienceDirect, Google Scholar, Cochrane Library, and ProQuest, covering publications from inception until June 2025. The search strategy combined both Medical Subject Headings (MeSH) and free-text keywords such as "vitamin D," "cholecalciferol," "ergocalciferol," "vitamin D supplementation," "breast cancer," "chemotherapy," "pathological complete response," "tumor response," "pathologic response," "treatment response," and "clinical outcomes." The strategy was developed in consultation with a health sciences librarian to ensure comprehensiveness, and manual screening of reference lists from relevant articles and systematic reviews was undertaken to identify additional eligible studies.

ELIGIBILITY CRITERIA

The eligibility criteria of this review were structured according to the PICOS framework. The target population consisted of adult women aged 18 years or older who had a confirmed diagnosis of breast cancer at any stage and were undergoing chemotherapy, including neoadjuvant, adjuvant, or palliative settings. Studies involving male breast cancer patients, individuals not receiving chemotherapy, or pediatric populations were excluded. The intervention of interest was vitamin D supplementation of any dose, frequency, or duration, administered concurrently with chemotherapy, either alone or in combination with other agents. Studies in which vitamin D was evaluated solely as prophylaxis for bone loss or in non-chemotherapy contexts, such as supplementation in postmenopausal women, were excluded. Acceptable comparators included placebo, no vitamin D supplementation, or chemotherapy alone, whereas studies without a comparator group or those comparing only different formulations or doses of vitamin D were excluded. Eligible outcomes encompassed a broad range of clinical endpoints, including tumor response (pCR, ORR), overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), treatment toxicity, safety, quality of life, serum vitamin D levels, nutrition status, inflammatory markers, and other relevant clinical outcomes. Studies reporting only molecular mechanisms without patient-level outcomes were excluded. Regarding study design, randomized controlled trials (RCTs), prospective or retrospective cohort studies, and case-control studies with extractable outcome data were considered eligible. Conversely, case reports, narrative reviews, letters, conference abstracts, in vitro or animal studies, and non-comparative observational studies were excluded.

Tab. 1 Eligibility Criteria Based on the PICOS Framework.

PICOS	Inclusion criteria	Exclusion criteria
Population (P)	Adult women (≥18 years) diagnosed with any stage of breast cancer undergoing chemotherapy (neoadjuvant, adjuvant, or palliative)	Studies involving male breast cancer patients, or those not undergoing chemotherapy, and pediatric populations
Intervention (I)	Vitamin D supplementation of any dose, frequency, and duration, administered concurrently with chemotherapy (alone or in combination with other agents)	Studies assessing vitamin D used only as a prophylactic against bone loss or for non-chemotherapy contexts (e.g., postmenopausal only)
Comparator (C)	Placebo, no vitamin D supplementation, or standard chemotherapy alone	Studies without a control group or comparison group; studies comparing different forms of vitamin D only
Outcomes (O)	Tumor response (pCR, ORR), overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), toxicity, safety, QoL, vitamin D level, nutrition status, inflammatory or treatment response markers, and other clinical outcomes	Studies not reporting clinical outcomes (e.g., reporting only molecular mechanisms without patient outcomes)
Study Design (S)	Randomized controlled trials (RCTs), prospective or retrospective cohort studies, or case-control studies with extractable data on outcomes	Case reports, review articles, letters, conference abstracts, in vitro or animal studies, and non-comparative observational studies.

SCREENING AND DATA EXTRACTION

Study eligibility was determined according to the predefined PICOS framework (Table 1). Initially, three reviewers independently screened titles and abstracts, followed by full-text evaluation. Any disagreements were resolved through consultation with a third reviewer. Data were then extracted into a standardized template, which included study characteristics (author, publication year, country, design, sample size), patient demographics (age), chemotherapy regimen, vitamin D dosage, comparator group, duration of follow-up, and reported outcomes. The outcomes of interest comprised tumor response (pCR or ORR), survival

endpoints (OS, DFS, PFS), toxicity, safety, quality of life, serum vitamin D levels, and inflammatory or treatment response markers. To ensure consistency, outcome definitions were harmonized across studies according to clinical and biochemical criteria.

QUALITY ASSESSMENT

To evaluate methodological quality, RCTs were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, covering domains such as randomization, allocation concealment, blinding, and outcome measurement. Observational studies were appraised with the Newcastle–Ottawa Scale (NOS). Three reviewers conducted the assessments independently, and any discrepancies were resolved by consensus.

RESULTS

LITERATURE SEARCH

The study selection process is summarized in the PRISMA flow diagram. A total of 770 records were identified through database searches (ScienceDirect, Cochrane, PubMed, ProQuest, and Google Scholar), of which 21 duplicates were removed. After screening 749 titles and abstracts, 691 records were excluded, leaving 58 articles for full-text assessment. Thirty reports could not be retrieved, and 28 were reviewed for eligibility. Of these, 22 were excluded for specific reasons, i.e., two due to an ineligible study design, as they were single-arm trials without a comparator group, and fourteen for lacking a relevant intervention, either because vitamin D supplementation was not provided or the focus was limited to baseline vitamin D status. Six for involving an ineligible population, as participants were not receiving chemotherapy. Ultimately, six studies fulfilled all inclusion criteria and were incorporated into the systematic review (Fig. 1).

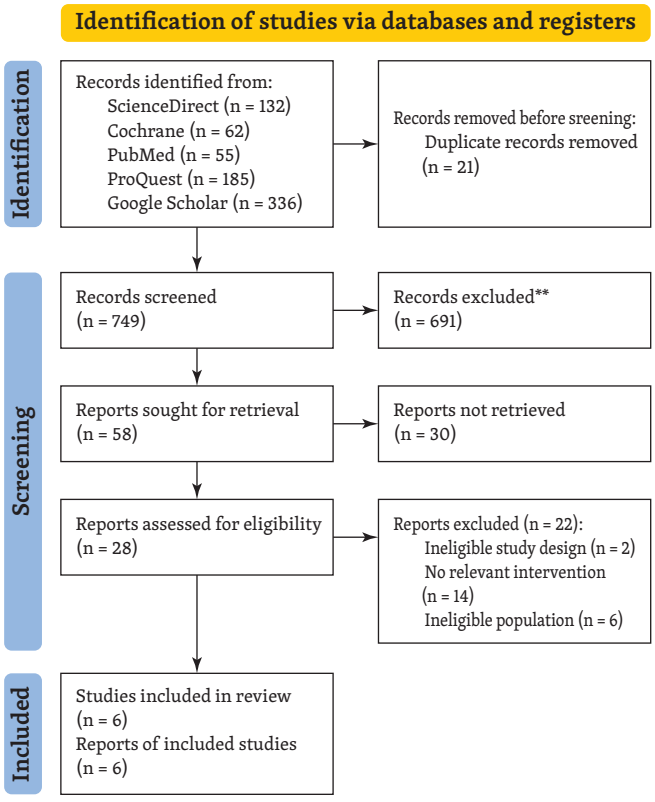

Fig. 1 PRISMA Flowchart.

STUDY CHARACTERISTICS

This systematic review included six studies that investigated the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy, with a primary focus on clinical outcomes. The included studies were conducted across diverse regions, including Palestine, Egypt, Brazil, Turkey, Iran, and the United States. They comprised different methodological approaches, such as randomized controlled trials, prospective randomized designs, double-blind clinical trials, and one retrospective cohort study.

The interventions assessed varied considerably, ranging from vitamin D monotherapy to a combination of vitamin D with synbiotics. Dosages of vitamin D also differed between trials, included 0.5 µg per day, 1000 IU daily, 2000 IU daily, and 50,000 IU once weekly, while one study primarily administered low doses of less than 10,000 IU per week. The control groups typically received standard care or a placebo.

Sample sizes extended from smaller trials with approximately 40 patients to larger cohorts with more than 200 participants. The age of participants spanned from the mid-40s to mid-50s, reflecting a population of middle-aged adults commonly diagnosed with breast cancer. Chemotherapy regimens across studies included adjuvant and neoadjuvant protocols, with some specifically using anthracycline-based therapies, cyclophosphamide, taxane regimens, or trastuzumab-containing combinations. Follow-up periods were heterogeneous, lasting from 9 weeks in the shortest trial to more than 40 months in the longest. Table 2 provides a detailed overview of the characteristics of the included studies.

STUDY OUTCOMES

The included studies evaluated the clinical outcomes of vitamin D supplementation in breast cancer patients undergoing chemotherapy. Primary outcomes mainly included nutritional status, tumor response (pCR, Ki-67, apoptosis), cardiotoxicity biomarkers (LDH, cTnT, IL-6), and disease-free survival. Secondary outcomes comprised adverse events, biochemical markers, overall survival, local recurrence, and inflammatory parameters (Table 3).

Almassri et al. investigated vitamin D supplementation (50,000 IU once weekly for 9 weeks) in patients with node-positive, hormone receptor-negative, and HER2-negative breast cancer, stage II-III, who received first-line Adriamycin-Cyclophosphamide (AC) chemotherapy over four cycles. Weekly vitamin D supplementation can improve the nutritional status of breast cancer patients undergoing therapy, as demonstrated by improvements in Patient-Generated Subjective Global Assessment (PG-SGA) scores, anthropometric parameters, blood albumin levels, and adequate energy and protein intake (22).

Tab. 2 Characteristics of the Included Studies

Authors, Year	Country	Study Design	Population	Total Sample	Age (years)	Chemotherapy	Intervention	Dosage of Vitamin D	Comparator	Follow-up Duration
Almassri et al., 2024[22]	Palestine	RCT (NCT05331807)	Patients with node-positive, hormone receptor-negative, and HER2-negative breast cancer, stage II–III, who received first-line Adriamycin-Cyclophosphamide (AC) chemotherapy over four cycles	44	47.3 (10.0) in intervention group, 47.3 (8.8) in control group	First-line Adriamycin-Cyclophosphamide (AC) chemotherapy	Vitamin D	50,000 IU once weekly	Standard care	9 weeks
El-Bassiouny et al., 2022[23]	Egypt	RCT	Patients with breast cancer who received four cycles of an adjuvant chemotherapy regimen (Doxorubicin and cyclophosphamide)	150	49 (6)	Adjuvant chemotherapy regimen (Doxorubicin and cyclophosphamide)	Vitamin D	0.5 µg once daily	Standard care	After four cycles of chemotherapy
Omodei et al., 2025[20]	Brazil	RCT	Patients with breast cancer who are undergoing neoadjuvant chemotherapy (NCT)	80	≥45	Neoadjuvant chemotherapy (NCT)	Vitamin D	2000 IU daily	Standard care	6 months
Ozkurt et al., 2025[21]	Turkey	Prospective RCT (NCT03986268)	Patients with primary breast cancer stage 1–3 who received neoadjuvant systemic therapy	227	46 (24–74)	Chemotherapy (Standard regimens of anthracyclines and/or taxanes with or without trastuzumab and/or pertuzumab)	Vitamin D	50,000 IU once a week	Standard care	41.4±18.9 weeks
Tirgar et al., 2024[24]	Iran	Double-blind, randomized clinical trial (IRCT20200313046756N1)	Patients with non-metastatic invasive breast cancer stage T1-3, N0-2 who received neoadjuvant chemotherapy	40	46.7 in the intervention group, 50 in the control group	Neoadjuvant chemotherapy	Vitamin D and synbiotics	1000 IU per day	Placebo	18 weeks
Zeichner et al., 2015[25]	United States	Retrospective cohort	Patients with HER2-positive non-metastatic breast cancer treated with trastuzumab-based chemotherapy	246	54 in the intervention group, 49 in the control group	Trastuzumab-based regimens (taxane ± anthracycline + trastuzumab)	Vitamin D	Mostly low dose (<10,000 IU/week)	Standard care	Median DFS follow-up 29.5 months, OS follow-up 40.2 months.

International unit (IU).

El-Bassioumy et al. investigated vitamin D supplementation (0.5 μg once until after four cycles of chemotherapy) in patients with breast cancer who received four cycles of an adjuvant chemotherapy regimen (doxorubicin and cyclophosphamide). Vitamin D supplementation in breast cancer patients undergoing adjuvant chemotherapy has been shown to reduce levels of inflammatory biomarkers (IL-6), LDH, and cTnT, while significantly increasing serum vitamin D levels compared to the control group (23).

Omodei et al. evaluated daily vitamin D supplementation (2000 IU daily for six months) in patients with breast cancer who were undergoing neoadjuvant chemotherapy (NCT). The intervention group demonstrated significantly higher pathological complete response (pCR) rates, increased serum 25(OH)D levels, and reduced adverse events compared to placebo (20).

Ozkurt et al. evaluated supplementation of 50,000 IU vitamin D once a week during neoadjuvant for around 41 weeks in patients with primary breast cancer stage 1–3 who received neoadjuvant systemic therapy. Vitamin D supplementation during neoadjuvant systemic treatment in breast cancer patients is associated with a significant increase in pCR, especially in patients with negative hormone receptor status and high Ki-67 expression (21).

Tirgar et al. investigated supplementation of 1000 IU per day of vitamin D in combination with synbiotics for 18 weeks in patients with non-metastatic invasive breast cancer who received neoadjuvant chemotherapy. Vitamin D supplementation, especially when combined with synbiotics, has shown potential anti-inflammatory effects in breast cancer patients undergoing neoadjuvant therapy, characterized by an increase in the anti-inflammatory index and prevention of IL-10 decline (24).

Zeichner et al. investigated vitamin D supplementation of mostly low doses (<10,000 IU/week) for 29.5–40.2 months in patients with HER2-positive non-metastatic breast cancer treated with trastuzumab-based chemotherapy. Vitamin D supplementation during neoadjuvant chemotherapy in breast cancer patients was associated with improved disease-free survival (DFS), although it did not show a significant difference in overall survival (OS) (25).

Tab. 3 Outcomes of the Included Studies.

Authors, Year	Primary Outcomes	Secondary Outcomes	Main Findings	Quality of the Study/ Risk of Bias
Almassri et al., 2024[22]	Nutritional status, blood albumin	Adverse events, urea, creatinine	Weekly vitamin D supplementation enhanced the nutritional status of the participants. Blood albumin levels significantly increased ($p<0.05$) in the vitamin D group as compared to the baseline.	Low risk of bias
El-Bassiouny et al., 2022[23]	Cardiotoxicity biomarkers (Lactate dehydrogenase (LDH), cardiac troponin T (cTnT), and anti-inflammatory Interleukin 6 (IL-6))	N.R.	Serum levels of LDH, cTnT, and IL-6 were significantly lower ($p<0.001$) in patients in the vitamin D group who took vitamin D supplements than in the control group.	Low risk of bias
Omodei et al., 2025[20]	Pathologic complete response (pCR)	N.R.	Compared to the placebo group, breast cancer patients undergoing NCT who took 2,000 IU of vitamin D supplements had a higher chance of experiencing a pathological complete response.	Low risk of bias
Ozkurt et al., 2025[21]	Pathologic complete response (pCR)	5-Year overall survival, disease-free survival, and Local-regional recurrence-free survival,	In patients with breast cancer, vitamin D supplementation during neoadjuvant systemic therapy significantly affects pCR.	Low risk of bias
Tirgar et al., 2024[24]	Pathologic complete response (pCR)	Inflammatory biomarkers, hormonal biomarkers, tumor proliferation marker (Ki-67)	Vitamin D and synbiotic supplementation showed potential anti-inflammatory effects but no apparent improvement in treatment response.	Low risk of bias
Zeichner et al., 2015[25]	Disease-free survival (DFS)	Overall survival (OS), tumor size, and lymphovascular invasion	Better DFS is linked to vitamin D supplementation in patients with non-metastatic HER2+ breast cancer.	High Quality

Not reported (N.R.); International unit (IU).

RISK OF BIAS

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias tool, with the results displayed in a bar chart (Fig. 2). Overall, the studies demonstrated a relatively strong methodological profile, as most domains were assessed as having a low risk of bias. Selection bias, including random sequence generation and allocation concealment, was generally well addressed, indicating that randomization procedures and allocation concealment methods were adequately implemented to reduce systematic differences between groups. Blinding of outcome assessments was also categorized mainly as low risk, supporting the reliability and objectivity of the outcomes measured. Conversely, performance bias related to blinding of participants and personnel was assessed as unclear in a small proportion of studies, likely reflecting limitations in reporting or practical difficulties in concealing intervention status to participants. A similar trend was observed in the other bias category, which showed the highest proportion of unclear risk, which could be due to factors such as small sample size, funding source, or other methodological limitations not covered by the standard domains. Both attrition bias and reporting bias were mainly categorized as low risk, although a small number of studies had insufficient information for a complete assessment. It is important to note that no domains were

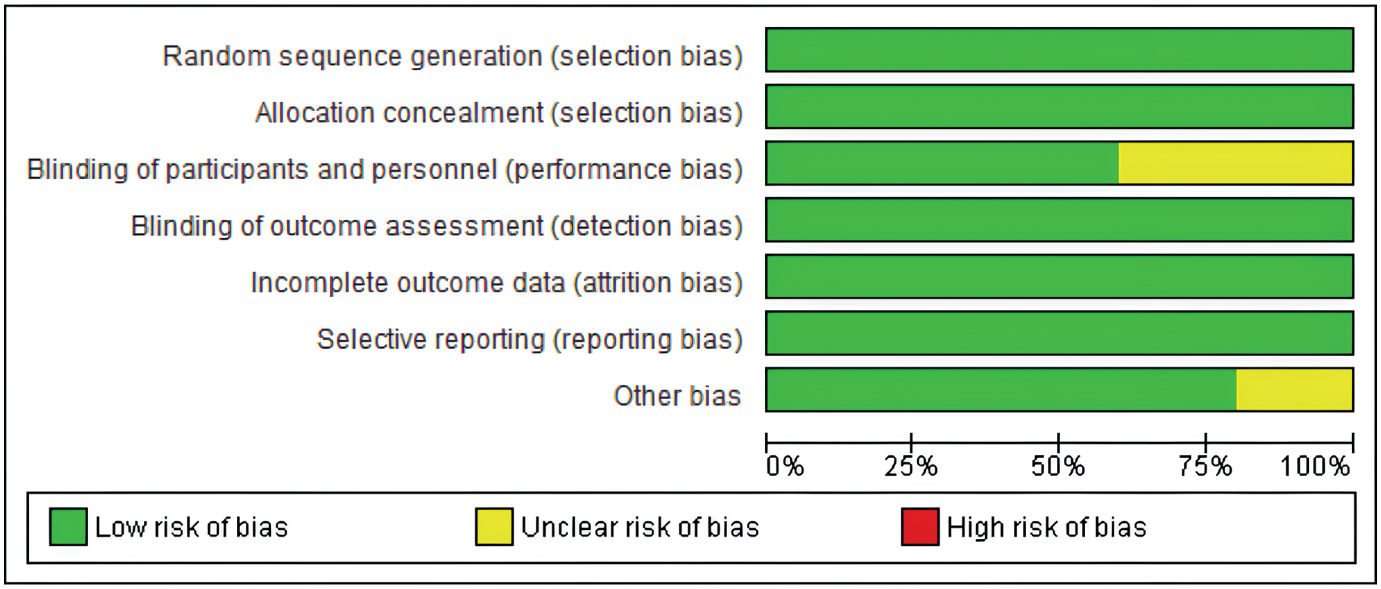

Fig. 2 Risk of bias graph.

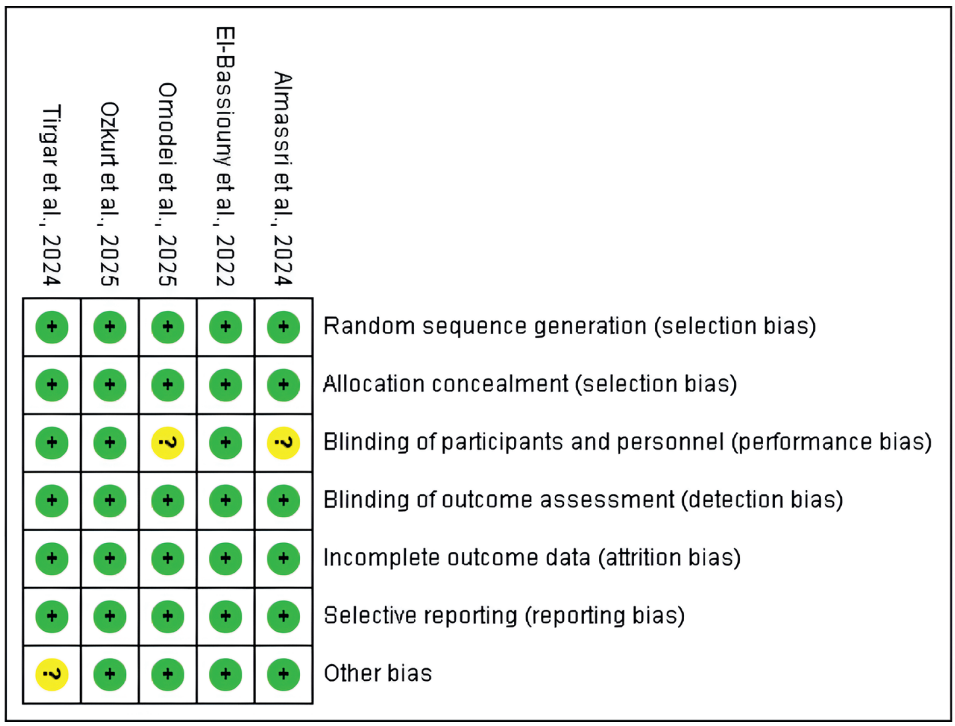

Fig. 3 Risk of bias summary.

assessed as high risk, so although there are some areas of uncertainty, the internal validity of the overall evidence can still be considered strong.

The risk of bias in the randomized controlled trials included in this review was evaluated using the Cochrane Risk of Bias Tool, with the results shown in the figure above. Overall, the methodological quality of the studies was quite good, as most domains were assessed as having a low risk of bias. Nearly all studies demonstrated low risk in the aspects of random sequence generation, blinding of outcome assessment, completeness of outcome data, and selective reporting, reflecting adherence to the basic principles of randomization and blinding to maintain internal validity. However, there were several domains with unclear risk assessments, such as allocation concealment in the studies of Almassri et al. (2024) and Omodei et al. (2025) due to a lack of information regarding methods for preventing allocation bias, and other bias in the study of Tirgar et al. (2024), which is likely related to design limitations such as small sample size or unreported external factors. Nevertheless, no studies were assessed as having a high risk in any domain. Hence, the overall risk of bias profile supports the reliability and robustness of the conclusions drawn from these studies (Figure 3).

DISCUSSION

The results of this systematic review indicate that vitamin D supplementation in breast cancer patients undergoing chemotherapy provides potential benefits in various clinical aspects. In terms of nutritional status, vitamin D supplementation has been shown to be associated with increased serum albumin levels, reflecting improvements in nutritional status and the body's anabolic response to disease stress and cytotoxic therapy (22). Vitamin D plays a role in regulating gene expression that controls cancer cell proliferation, differentiation, and apoptosis, and modulates the immune system, thereby reducing inflammation that contributes to cachexia and malnutrition (26–28). Furthermore, vitamin D deficiency is often associated with fatigue, pain, gastrointestinal disturbances, and decreased appetite. Vitamin D supplementation has been shown to improve these symptoms, increase energy and protein intake, and improve PG-SGA scores and anthropometric parameters (29–31). These effects are also associated with increased serum albumin levels, as improved nutrient intake and suppressed inflammation promote hepatic protein synthesis and decrease albumin degradation (32).

In addition, vitamin D supplementation can also reduce inflammatory biomarkers such as interleukin-6 (IL-6), lactate dehydrogenase (LDH), and cardiac damage biomarkers such as cardiac troponin T (cTnT), which often increase due to chemotherapy toxicity (23). Vitamin D supplementation can suppress the increase in inflammatory biomarkers and tissue damage that arise due to chemotherapy toxicity through several integrated mechanisms, molecularly, the active ligand of vitamin D [1,25-$(OH)_2D_3$] binds to the vitamin D receptor (VDR) which then inhibits pro-inflammatory transcription pathways such as by interfering with the activation of NF-κB and the JAK/STAT pathway, thereby reducing the production of pro-inflammatory cytokines such as IL-6 (33). Reducing IL-6 and other inflammatory mediators will minimize cytokine stress in various tissues and decrease the release of tissue markers released during cell damage, thereby directly reducing measurable IL-6 concentrations (34). Observational studies report an inverse relationship between vitamin D status and LDH levels such that improved vitamin D status is associated with lower LDH, possibly through reduced inflammation and metabolic stabilization of cells (35). For cardiac markers such as cTnT, there is plausible biological evidence that reduction of systemic inflammation and direct protective effects on endothelial cells may reduce chemotherapy-induced troponin release (23, 36).

From the tumor response perspective, vitamin D supplementation is associated with increased pathological complete response (pCR) rates in patients receiving neoadjuvant chemotherapy, as well as increasing the apoptotic index and suppressing cancer cell proliferation (20, 21, 24). Moreover, one of the included studies also reported a positive association between higher vitamin D levels and disease-free survival (DFS) (25). These findings support the growing recognition of vitamin D as a potential chemosensitizer in cancer therapy. Vitamin D supplementation may improve pCR in patients receiving neoadjuvant chemotherapy through several interrelated molecular and tumor microenvironmental mechanisms. Intracellularly, the active form of vitamin D binds to the vitamin D receptor and alters the transcription of target genes that regulate the cell cycle, decreasing proliferation markers and shifting the balance of apoptotic proteins toward pro-apoptotic ones (e.g., ↑BAX, ↓BCL-2), thereby enhancing the cytotoxic effects of chemotherapy (37). In addition, activation of the VDR pathway increases the response to DNA damage so that tumors become less efficient at repairing damage induced by chemotherapeutic agents, resulting in increased chemotherapeutic apoptosis (38). At another cellular level, vitamin D also modulates autophagy and suppresses pro-survival signals and pro-angiogenesis pathways that support tumor growth, so that the combination with chemotherapy is synergistic and reduces the ability of tumors to survive (39). In colorectal cancer, vitamin D enhances the sensitivity of cancer cells to chemotherapy when combined with secreted protein acidic and rich in cysteine. This protein up-regulates the vitamin D receptor. This combination significantly reduces cell viability and enhances chemotherapy-induced apoptosis in therapy-resistant colorectal cancer cells (40). These combined mechanisms may also ultimately reduce the risk of disease recurrence and progression, which is reflected in increased DFS.

Previous study in other cancer populations, such as colorectal cancer, have shown that higher 25(OH)D levels are significantly associated with improved overall survival and CRC-specific survival (41). Other study involving various cancer populations have shown similar results, namely that vitamin D plays an important role in preventing the side effects of neoadjuvant radiotherapy and chemotherapy, including helping to reduce symptoms such as nausea, vomiting, and fatigue due to aggressive therapy (42).

These findings carry important clinical implications. Screening for vitamin D status in breast cancer patients should be considered at baseline, given the high prevalence of vitamin D deficiency in this population. Vitamin D supplementation has the potential to serve as an adjunctive therapy to improve clinical outcomes, both in terms of tumor response and patient quality of life. However, current international guidelines do not yet recommend its routine use in oncology practice. The strength of the available evidence primarily derives from randomized clinical trials assessing relevant outcomes, including pathological complete response (pCR), inflammatory biomarkers, and nutritional parameters, which collectively demonstrate the significant role of vitamin D in cancer therapy. This study is the first to specifically focus on the effects of vitamin D supplementation in breast cancer patients undergoing chemotherapy, thereby contributing novel insights to the field. Nevertheless, limitations such as variation in dosage and duration, heterogeneity of study designs, small sample sizes, and follow-up generally limited to the end of chemotherapy, warrant cautious interpretation of the results.

CONCLUSION

Current evidence suggests that vitamin D supplementation in breast cancer patients undergoing chemotherapy may provide various benefits on clinical outcomes, including improved nutritional status, decreased biomarkers of inflammation and cardiotoxicity, and increased pathological complete response (pCR) and disease-free survival (DFS). These findings support the potential of vitamin D as a beneficial adjuvant therapy. Therefore, large-scale randomized controlled trials with standardized designs, evaluation of optimal dosing, and stratification based on stage, molecular subtype, and baseline vitamin D levels are needed. Furthermore, long-term studies are essential to determine the impact of supplementation on OS and DFS in a comprehensive manner, thereby strengthening the scientific evidence base supporting its integration into breast cancer management.

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CTCAE-Guided Management of Cytotoxic Chemotherapy Toxicity in Uro-Oncology: A Contemporary Narrative Review

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ABSTRACT

Cytotoxic chemotherapy remains integral to contemporary uro-oncology despite the rapid expansion of targeted therapy, antibody-drug conjugates, and immunotherapy. Its role is especially critical where therapeutic success depends on maintaining adequate dose intensity, most notably in metastatic testicular germ cell tumours and in cisplatin-based perioperative treatment for muscle-invasive bladder cancer. In metastatic prostate cancer and selected penile squamous cell carcinoma, taxane- and platinum-based regimens also retain clinical value but are constrained by hematologic, neurologic, renal, pulmonary, and gastrointestinal toxicities. This narrative review summarises current evidence and guideline recommendations for Common Terminology Criteria for Adverse Events (CTCAE)-guided management of chemotherapy toxicity across major uro-oncologic disease settings. A practical emphasis is placed on pretreatment risk stratification, cycle-by-cycle surveillance, supportive care, and intent-adapted treatment modification. Across tumour types, early recognition of grade 2 toxicity, urgent management of febrile neutropenia and organ toxicity, and thoughtful preservation of dose intensity when cure is realistic are the central management principles. In older, frail, immunosuppressed, heavily pretreated, or organ-limited patients, CTCAE grades must be interpreted against baseline reserve and cumulative toxicity.

KEYWORDS

uro-oncology; CTCAE; chemotherapy toxicity; germ cell tumour; urothelial carcinoma; prostate cancer; penile cancer

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INTRODUCTION

Although uro-oncology is increasingly shaped by precision medicine and immunotherapy, conventional cytotoxic chemotherapy remains indispensable in several major disease states. In metastatic testicular germ cell tumours, cisplatin-based treatment remains one of the clearest examples of curative systemic therapy in solid oncology (1–3). In muscle-invasive and metastatic urothelial carcinoma, platinum-based chemotherapy continues to define perioperative and first-line systemic treatment for appropriately selected patients (4–7). In metastatic prostate cancer, docetaxel and cabazitaxel remain clinically important across hormone-sensitive and castration-resistant settings (8–12). In penile squamous cell carcinoma, cisplatin- and taxane-based regimens still have a role in selected men with bulky nodal disease (13, 14).

The clinical problem is not only whether chemotherapy should be used, but whether it can be delivered safely and on schedule. Many of the most effective regimens in uro-oncology are also among the most toxic. Platinum agents challenge renal function, hearing, and peripheral nerves; bleomycin can injure the lung; taxanes produce marrow suppression, neuropathy, and nail toxicity; and multidrug combinations create overlapping risks of infection, dehydration, and hospitalisation.

The Common Terminology Criteria for Adverse Events (CTCAE) evolved from the National Cancer Institute Common Toxicity Criteria, introduced primarily to standardise adverse-event reporting in clinical trials. Over successive versions, the framework expanded from a research reporting instrument into a shared language that is also routinely used to structure bedside assessment, interprofessional communication, protocol-defined dose modification, and supportive care (15).

CTCAE version 6.0, released by the National Cancer Institute in 2025, retains the familiar five-grade framework but updates the terminology to MedDRA 28.0 and addresses specific limitations of version 5.0. The principal improvements highlighted by the National Cancer Institute include grading adverse events in patients with abnormal baseline laboratory values, better characterisation of events associated with immunotherapeutics, and refined categorisation of cardiac adverse events. A comprehensive mapping of term-and-grade combinations from version 5.0 to version 6.0 was also developed to support implementation and longitudinal comparison (16, 17). Although the present review focuses on cytotoxic chemotherapy, these changes are clinically relevant because they improve baseline-aware interpretation and reduce ambiguity when patients receive sequential or combined systemic treatments.

The aim of this review is to summarise contemporary evidence for CTCAE-guided management of cytotoxic chemotherapy toxicity in uro-oncology, with emphasis on disease-specific priorities, cross-cutting toxicity domains, and a practical intent-adapted approach to treatment continuation, delay, modification, or discontinuation. Its intended contribution is an integrated framework spanning multiple uro-oncologic disease settings rather than a catalogue of isolated drug-specific adverse events.

MATERIAL AND METHODS

This article was prepared as a narrative review. The core conceptual framework was based on CTCAE version 6.0 (16), the 2026 European Association of Urology (EAU) guidelines for testicular cancer, muscle-invasive and metastatic bladder cancer, prostate cancer, and penile cancer (1, 4, 8, 13), and contemporary supportive-care recommendations for chemotherapy-induced nausea and vomiting and febrile neutropenia (18, 19).

Landmark clinical studies were selected when they materially shaped current regimen choice, toxicity expectations, or supportive-care decision making in uro-oncology (2, 3, 5–7, 9–12, 14, 20–23). Additional cross-cutting literature was reviewed for older and frail adults, baseline immunosuppression, cumulative toxicity, and impaired organ reserve. The scope of the review was restricted to cytotoxic chemotherapy and immediately related supportive care. Immunotherapy, targeted therapy, and antibody-drug conjugates were discussed only when necessary to contextualise the continuing role of chemotherapy in current practice.

RESULTS

ROLE OF CTCAE V6.0 IN URO-ONCOLOGY

CTCAE version 6.0 preserves the familiar five-grade severity framework while refining adverse-event definitions and maintaining a clinically intuitive hierarchy from mild toxicity to treatment-related death (16, 17). In practical uro-oncology, the utility of CTCAE lies in the fact that the action threshold often sits at grade 2 rather than grade 3. Waiting until organ toxicity, neuropathy, dehydration, or cytopenia becomes severe is rarely good bedside management when curative or survival-prolonging treatment depends on schedule adherence.

CTCAE is most useful when interpreted in the context of treatment intent. For example, a moderate creatinine rise during neoadjuvant cisplatin for muscle-invasive bladder cancer should trigger vigorous supportive intervention and short-interval reassessment rather than immediate abandonment of cisplatin. By contrast, recurrent grade 2 or irreversible grade 3 neuropathy during later-line palliative taxane therapy may justify earlier dose reduction or discontinuation. Proper CTCAE-based grading therefore improves both reproducibility and the quality of clinical judgement (Table 1).

Tab. 1 Contemporary chemotherapy platforms in uro-oncology and their dominant toxicity priorities.

Disease setting	Core cytotoxic regimens still relevant in practice	Typical treatment intent	Dominant toxicity concerns	Key baseline assessments
Metastatic testicular GCT	BEP; EP	Curative	Nephrotoxicity, bleomycin pneumonitis, neuropathy/ototoxicity, febrile neutropenia, fertility and vascular late effects	Complete blood count, creatinine/eGFR, magnesium, pulmonary history, neuropathy/hearing history, fertility counselling
Muscle-invasive / metastatic urothelial carcinoma	dd-MVAC; gemcitabine-cisplatin; selected carboplatin-based alternatives	Perioperative survival gain or palliative disease control	Renal injury, febrile neutropenia, mucositis, severe CINV, neuropathy/ototoxicity	Performance status, creatinine clearance, complete blood count, hydration status, neuropathy/hearing assessment
Metastatic prostate cancer	Docetaxel; cabazitaxel	Disease control / survival prolongation	Neutropenia, febrile neutropenia, fatigue, neuropathy, nail toxicity, diarrhoea	Complete blood count, infection risk, functional status/frailty, bowel function, neuropathy history
Bulky nodal penile squamous cell carcinoma	TIP; other cisplatin-taxane combinations in expert centres	Neoadjuvant downstaging	Myelosuppression, nephrotoxicity, neuropathy, emesis, ifosfamide-related complexity	Complete blood count, renal function, infection status, performance status, neuropathy screen

Abbreviations: BEP = bleomycin, etoposide, cisplatin; CINV = chemotherapy-induced nausea and vomiting; dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; eGFR = estimated glomerular filtration rate; EP = etoposide, cisplatin; GCT = germ cell tumour; TIP = paclitaxel, ifosfamide, cisplatin.

DISEASE-SPECIFIC TOXICITY PRIORITIES

Metastatic testicular germ cell tumours

Metastatic germ cell tumours remain the prototypical curable malignancy treated with systemic chemotherapy. Current management continues to be anchored in the International Germ Cell Cancer Collaborative Group risk framework and in cisplatin-based regimens such as bleomycin, etoposide, and cisplatin (BEP) or etoposide and cisplatin (EP) (1–3). Because cure is realistic even in advanced disease, preservation of dose intensity is a central management principle.

Renal toxicity, hypomagnesaemia, peripheral neuropathy, ototoxicity, and febrile neutropenia are the most frequent treatment-limiting events. Prevention of cisplatin nephrotoxicity requires structured hydration, magnesium replacement, review of concomitant nephrotoxins, and early correction of vomiting or diarrhoea; contemporary evidence continues to support the renoprotective role of magnesium supplementation during cisplatin treatment (20). Bleomycin pulmonary toxicity remains the most characteristic germ-cell-tumour-specific complication and should be suspected early in the presence of cough, dyspnoea, or new interstitial changes (21). In this disease, supportive care is not separate from curative therapy; it is a prerequisite for cure.

Muscle-invasive and metastatic urothelial carcinoma

In urothelial carcinoma, toxicity management begins with patient selection. The classic concept of cisplatin unfitness remains clinically useful and incorporates impaired renal function, poor performance status, clinically meaningful neuropathy or hearing loss, and severe cardiac comorbidity (4, 6). Even as perioperative strategies evolve, contemporary practice continues to rely on cisplatin-based chemotherapy in appropriately selected fit patients.

The toxicity phenotype varies by regimen. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) with growth-factor support remains an important perioperative option but requires close surveillance, whereas gemcitabine-cisplatin is generally better tolerated than classic MVAC and remains foundational in advanced disease (4, 5, 7). Renal injury, mucositis, severe chemotherapy-induced nausea and vomiting, and febrile neutropenia are the dominant practical concerns. In curative-intent treatment, a short delay for renal optimisation is often preferable to premature dose fragmentation or inappropriate substitution.

Metastatic prostate cancer

Cytotoxic therapy in metastatic prostate cancer is dominated by taxanes. Docetaxel remains a standard option in selected men with metastatic hormone-sensitive disease and in metastatic castration-resistant prostate cancer, while cabazitaxel retains a key role after docetaxel exposure, particularly in patients progressing on androgen receptor pathway inhibitors (8–12).

The major dose-limiting toxicity of taxanes is marrow suppression, especially neutropenia and febrile neutropenia. Primary granulocyte colony-stimulating factor prophylaxis is therefore recommended or strongly considered in appropriate cabazitaxel-treated patients (8, 10–12). Peripheral neuropathy, fatigue, nail toxicity, and diarrhoea are the other clinically relevant toxicities. Emerging supportive-care data suggests that extremity cooling may reduce taxane-related nail changes and peripheral neuropathy and may be considered where available (22, 23).

Penile squamous cell carcinoma

Penile squamous cell carcinoma is rare, and the evidence base for chemotherapy is correspondingly limited. Nevertheless, contemporary guidelines continue to support neoadjuvant cisplatin- and taxane-based treatment in selected fit men with bulky mobile inguinal nodes or pelvic nodal disease, ideally in experienced centres (13).

The best-known prospective evidence comes from the phase II TIP regimen study, in which paclitaxel, ifosfamide, and cisplatin enabled meaningful downstaging and subsequent surgery in a substantial subset of patients (14). The toxicologic burden is considerable, combining myelosuppression, nephrotoxicity, neurotoxicity, emesis, and the supportive-care complexity of ifosfamide. In this setting, CTCAE-based prospective grading and a clearly defined toxicity plan before the first cycle are particularly important.

Cross-cutting toxicity domains

Several toxicities recur across uro-oncologic regimens and deserve a unified management strategy. Febrile neutropenia must always be treated as an oncologic emergency. CTCAE-based classification supports immediate escalation to cultures, empiric broad-spectrum antibiotics, haemodynamic assessment, and risk-adapted inpatient or outpatient management (16, 19).

Nephrotoxicity should be anticipated rather than discovered late. Cisplatin-associated kidney injury is often preceded by reduced oral intake, persistent emesis, orthostasis, and hypomagnesaemia. The most effective response pathway combines CTCAE laboratory thresholds with clinical context, structured hydration, and active medication review, particularly for non-steroidal anti-inflammatory drugs and renin-angiotensin system inhibitors (16, 20).

Pulmonary toxicity during bleomycin treatment requires a low threshold for intervention. Similarly, cumulative peripheral sensory neuropathy and ototoxicity should be documented longitudinally because reversal is often incomplete once clinically significant deficits are established (16, 21). Nausea, vomiting, mucositis, and diarrhoea should be viewed as operational toxicities because they disrupt hydration, nutrition, treatment adherence, and the ability to maintain dose intensity. Guideline-concordant antiemetic prophylaxis should therefore be implemented from the first cycle rather than after the first severe episode (18) (Table 2).

Tab. 2 CTCAE-oriented management matrix for high-impact chemotherapy toxicities in uro-oncology.

High-impact toxicity	Representative CTCAE v6.0 trigger(s)	Preferred action in curative-intent therapy	Preferred action in palliative therapy	Clinical notes
Creatinine increased / renal toxicity	Grade 2: >1.5–3.0 × upper limit of normal; grade 3: >3.0–6.0 × upper limit of normal	Urgent hydration and electrolyte review, hold treatment if persistent, re-challenge only after meaningful recovery	Lower threshold for regimen modification or agent switch	Always review vomiting, diarrhoea, nephrotoxic drugs, and magnesium depletion
Neutrophil count decreased / febrile neutropenia	Grade 3–4 neutropenia; febrile neutropenia = fever with absolute neutrophil count <1.0 × 10^9/L	Immediate sepsis-oriented management; prefer delay plus supportive care over empiric dose erosion when cure is realistic	Immediate management, then consider dose reduction or prophylactic G-CSF if treatment continues	Febrile neutropenia is an emergency, not a routine adverse effect
Peripheral sensory neuropathy	Grade 2 limits instrumental activities of daily living; grade 3 limits self-care activities	Escalate monitoring at grade 2; modify therapy only if persistent, progressive, or function-threatening	Dose reduction or discontinuation is appropriate earlier if function or quality of life is compromised	Document symptoms longitudinally rather than relying on a single yes/no question
Pulmonary toxicity during bleomycin	New cough, dyspnoea, imaging changes, or oxygen requirement	Stop bleomycin promptly, investigate, and treat; do not wait for advanced respiratory compromise	Usually discontinue the offending agent permanently	Clinical suspicion matters even before dramatic imaging abnormalities appear
Nausea, vomiting, and dehydration	Recurrent vomiting, poor oral intake, electrolyte loss, or hospital attendance	Optimise full antiemetic prophylaxis and hydration to preserve schedule intensity	Optimise symptom control; treatment breaks or de-escalation may be appropriate earlier	The downstream problem is often kidney injury and treatment delay rather than nausea alone

Practical CTCAE workflow

A practical CTCAE-guided workflow in uro-oncology has four major steps: define therapeutic intent before treatment begins, map baseline vulnerability, grade every relevant toxicity prospectively before each cycle, and match the intervention to both CTCAE grade and oncologic stakes. Responsibility for this pathway is shared: urologists define disease-specific and surgical priorities; medical oncologists lead systemic-treatment selection, dose modification, and treatment re-challenge; and oncology pharmacists, specialist nurses, and organ-specific consultants support prevention, monitoring, and toxicity management. In curative-intent therapy, grade 1 toxicity generally permits treatment continuation with reinforced supportive care; persistent or escalating grade 2 toxicity usually requires intensified intervention and often a brief delay; grade 3 toxicity typically requires treatment interruption and expert reassessment before resumption; and grade 4 toxicity usually mandates discontinuation of the offending agent unless an exceptional rationale for modified continuation exists (1, 4, 8, 13, 16).

In palliative settings, the same CTCAE grades apply, but the tolerance for repeated grade 2 or irreversible grade 3 toxicity should be lower because quality of life and preservation of function become dominant clinical objectives. The central principle is early detection, proportionate action, and transparent re-evaluation before the next cycle (Figure 1).

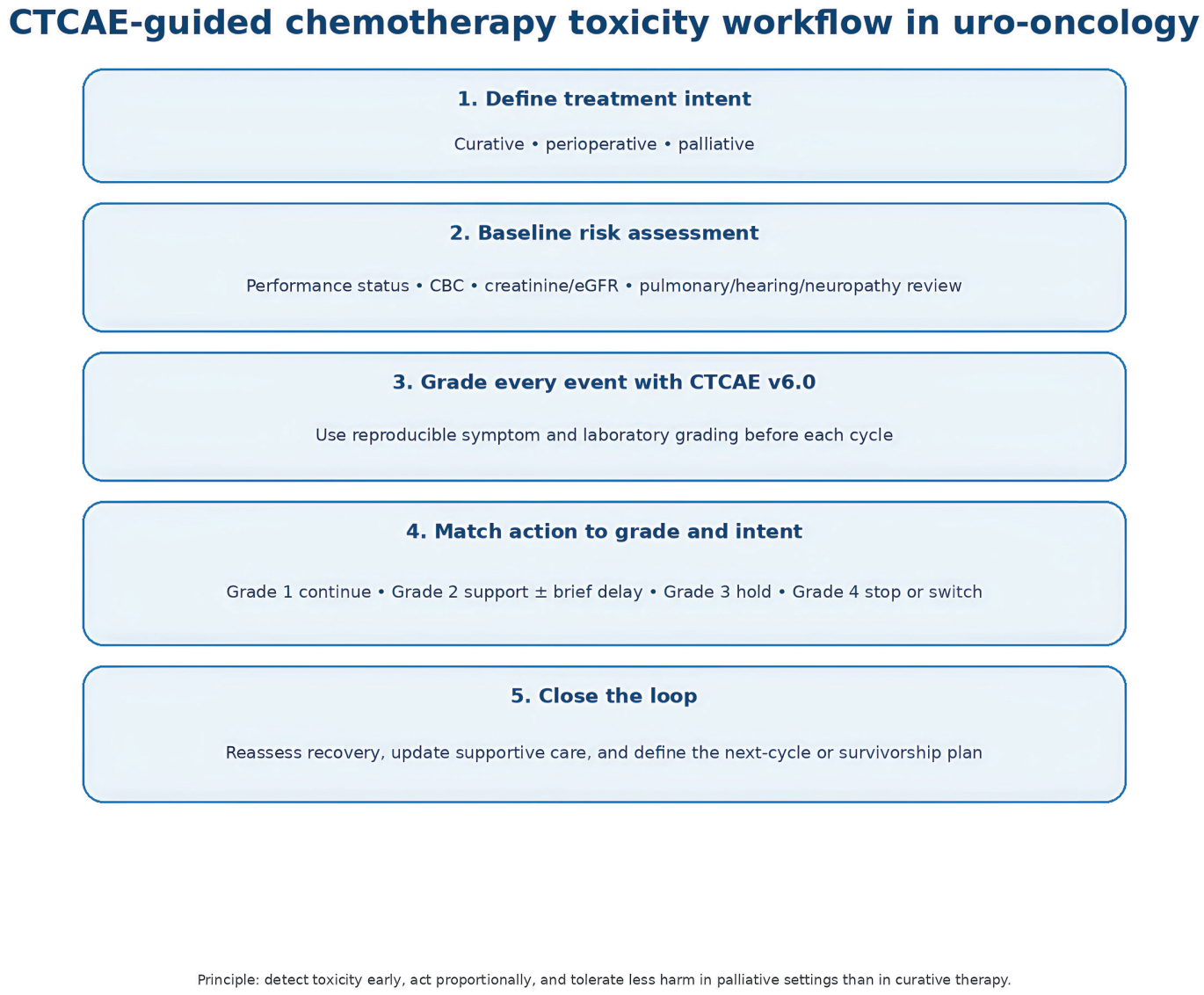

Fig. 1 Intent-adapted CTCAE workflow for chemotherapy toxicity management in uro-oncology.
The figure summarises a practical sequence: defines therapeutic intent, assess baseline vulnerability, grade toxicities prospectively, match the intervention to CTCAE grade and oncologic stakes, and reassess before the next cycle or survivorship planning.

Special patient populations and baseline vulnerability

CTCAE grade describes event severity but does not, by itself, describe physiologic reserve. The same grade 2 diarrhoea, fatigue, or neutropenia may have very different consequences in a fit young patient and in an older adult with frailty, falls, polypharmacy, cognitive impairment, malnutrition, or limited social support. For adults aged 65 years and older, a geriatric assessment covering physical function, cognition, nutrition, comorbidity, medications, psychological status, and social support should complement performance status. Vulnerabilities identified before chemotherapy should lead to targeted interventions, closer early-cycle surveillance, and, when appropriate, proactive regimen or supportive-care adaptation rather than reflexive undertreatment based on chronological age alone (24).

Patients with borderline renal, hepatic, marrow, cardiac, or pulmonary reserve require baseline values to be treated as part of the toxicity definition. A post-treatment result that remains within the population reference range can still represent a clinically meaningful decline from baseline, whereas a stable chronic abnormality should not automatically be attributed to chemotherapy. Drug-specific pharmacokinetics measured or appropriately estimated renal function, hepatic impairment, interacting medicines, and the reversibility of the deficit should guide re-challenge and dose selection (16, 17, 25). In heavily pretreated patients, cumulative neuropathy, ototoxicity, marrow exhaustion, and prior organ injury should be documented longitudinally; the decision threshold should reflect trajectory and functional effect, not only the highest grade recorded during the current cycle (26).

Baseline immunosuppression – because of solid-organ transplantation, autoimmune disease, prolonged corticosteroid exposure, or other causes – adds infection risk, drug–drug interactions, and, in transplant recipients, the competing risks of graft dysfunction and rejection. Evidence is limited and these patients are frequently excluded from prospective trials; chemotherapy should therefore be planned jointly with medical oncology and the relevant organ or transplant specialist, with explicit antimicrobial, interaction, and therapeutic-drug-monitoring plans where indicated (27). Across all special populations, CTCAE should function as a common language within a multidisciplinary team rather than as an automatic dose-reduction algorithm.

DISCUSSION

Across contemporary uro-oncology, the same management tension recurs: clinicians must control toxicity without unnecessarily compromising effective therapy. CTCAE offers a reproducible language for doing so, but its value depends on disciplined application. A grading system alone does not improve outcomes; improvement comes from linking grades to predefined clinical actions, documenting events prospectively, and interpreting them in light of therapeutic intent, baseline reserve, cumulative exposure, and patient priorities. Because these decisions frequently intersect with surgery, systemic therapy, infection management, and organ-specific care, they should be made within an explicit multidisciplinary framework that includes urology and medical oncology.

The practical implication is straightforward. In disease settings where cure or major survival gain is realistic, especially metastatic germ cell tumours and cisplatin-based perioperative therapy for urothelial carcinoma, supportive care should be used aggressively to preserve treatment intensity whenever clinically defensible. In later-line palliative therapy, especially taxane-based treatment in metastatic prostate cancer, repeated moderate toxicity may appropriately trigger earlier de-escalation. For older, frail, immunosuppressed, heavily pretreated, or organ-limited patients, the same nominal CTCAE grade may justify a different intervention because the probability and consequences of further deterioration are not equivalent. A CTCAE-guided approach is therefore not a rigid algorithm but a structured platform for intent- and vulnerability-adapted decision making.

This review has the limitations inherent to a narrative synthesis. It does not provide a formal systematic review or meta-analysis, and several recommendations necessarily reflect interpretation of guideline-based practice rather than direct comparative trials. Nevertheless, the central clinical message remains robust: consistent toxicity grading, careful baseline assessment, and early supportive intervention are essential components of safe and effective chemotherapy delivery in uro-oncology.

CONCLUSIONS

CTCAE version 6.0 provides a practical framework for modern toxicity management in uro-oncology. Its main value lies in improving reproducibility, multidisciplinary communication, and the timing of intervention, while its updated baseline-aware and terminology refinements improve interpretation across increasingly complex systemic-treatment pathways.

Across metastatic germ cell tumours, urothelial carcinoma, metastatic prostate cancer, and penile cancer, the critical question is rarely whether toxicity exists, but whether it is recognised early enough and managed in a way that matches the oncologic stakes. A CTCAE-guided and intent-adapted strategy should therefore be regarded as a core component of chemotherapy practice rather than ancillary supportive care.

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The Changing Comorbidity Burden and its Association with Outcomes in Acute NIV: A Charlson Comorbidity Index-Based Analysis

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ABSTRACT

Acute non-invasive ventilation (NIV) is a lifesaving treatment for acute hypercapnic respiratory failure, particularly during exacerbations of chronic obstructive pulmonary disease (COPD), and is also an established therapy that improves outcomes in acute cardiogenic pulmonary oedema. Decisions regarding NIV initiation are complex and require careful consideration of patient-specific factors. With an aging population, with increasing multimorbidity, understanding the evolving acute NIV patient characteristics is critical to optimize NIV delivery.

We audited all adult acute NIV patients at a tertiary centre, pre-COVID (April 2019–March 2020) and post-COVID (April 2023–March 2024) and performed a retrospective observational cohort analysis. We compared the Charlson Comorbidity Index (CCI) scores and outcomes using Chi-squared or Mann-Whitney U.

Three hundred and twelve patients received acute NIV, 171 pre-COVID and 141 post-COVID. Post-COVID patients had higher comorbidity burden vs pre-COVID (median CCI 5 vs 4, p=0.002), and ward-based NIV ceiling of care frequency (83% vs 66%, p=0.009). Across the entire cohort, higher CCI score associated with increased NIV failure (p=0.007) and in-hospital mortality (p<0.001).

Our demonstration of increasing multimorbidity in a real-world cohort, and the association of multimorbidity with NIV failure, provides insights to guide optimization strategies for acute NIV services. Further understanding the evolving patient characteristics and their impact on outcome is essential to determine how best to incorporate comorbidity assessment into clinical decision making for improved NIV delivery.

KEYWORDS

non-invasive ventilation; COPD; exacerbations; comorbidity; Charlson Comorbidity Index

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BRIEF COMMUNICATION

Acute non-invasive ventilation (NIV) is a lifesaving treatment for acute hypercapnic respiratory failure, particularly during exacerbations of chronic obstructive pulmonary disease (COPD) (1) and is also an established therapy that improves outcomes in acute cardiogenic pulmonary oedema (2). Decisions regarding NIV initiation are complex and require careful consideration of patient-specific factors, including expected treatment tolerance, benefit and overall prognosis (3). With an aging population with increasing multimorbidity, understanding the evolving characteristics of patients receiving acute NIV, and their impact on clinical trajectory, is essential to optimize delivery, guide service development and improve patient outcomes.

Since the coronavirus disease 2019 (COVID-19) pandemic, acute NIV services have undergone marked changes (3, 4). However, the impact of evolving comorbidity burden on outcomes remains poorly understood. We aimed to characterise the comorbidity burden among patients requiring acute non-invasive ventilation before and after the COVID-19 pandemic and assess its association with clinical outcomes. By doing this we sought to provide real-world data to better understand the evolving cohort of patients receiving acute NIV in the United Kingdom, with the aim of informing the future organisation and development of acute NIV services.

We audited all adult patients treated with acute NIV at a tertiary centre during two periods – pre-COVID (April 2019–March 2020) and post-COVID (April 2023–March 2024). We performed a retrospective observational cohort analysis of existing data. This data had previously been collected as part of a clinical audit which had been registered within our National Health Service Institution's Clinical Audit Registration and Management System (CARMS; registration number CARMS-19085). Demographic, clinical, and outcome data for each group were assessed and the Charlson Comorbidity Index (CCI) was calculated (5). The CCI is an established clinical scoring system for comorbidity which has been shown to be inversely proportional to the estimated 10-year survival and has utility in classifying prognostic comorbidity in longitudinal studies. This score is calculated based on a patient's age and the presence of the following comorbidities: prior myocardial infarction, congestive heart failure, peripheral vascular disease, prior cerebrovascular accident or transient ischaemic attack, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumour, leukaemia, lymphoma and acquired immunodeficiency syndrome (AIDS) (5). We compared the Charlson Comorbidity Index (CCI) scores and clinical outcomes using non-parametric tests, Chi-squared or Mann-Whitney U. NIV failure was defined as either NIV being withdrawn, or the requirement for intubation, due to clinical deterioration on NIV.

A total of 312 patients received acute NIV across both time periods, 171 pre-COVID and 141 post-COVID. Baseline demographics were similar, including median age, 60.2 and 58.2, and percentage female, 68.0% and 70.0%, respectively (Table 1). Patients in the post-COVID cohort had a significantly higher comorbidity burden vs the pre-COVID cohort (median CCI 5 vs 4, p=0.002), and more frequntly had a ward-based NIV ceiling of care (83% vs 66%, p=0.009). Across the entire cohort, a higher CCI score was associated with increased NIV failure risk (p=0.007) and in-hospital mortality (p<0.001). Despite this, overall, NIV success (75.0% vs 72.0%, p=0.521) and in-hospital mortality (22% vs 26%, p=0.408) were similar between cohorts.

This shift towards more complex multimorbid patients receiving acute NIV is clinically relevant, particularly given the association of CCI scores with adverse outcomes. The absence of a corresponding increase in NIV failure rates or mortality during this period may reflect wider hospital factors, including improvements in clinical practice, service organization, and the impact of quality improvement initiatives (3, 6–13). Incorporating comorbidity assessment into early clinical evaluation may enhance risk stratification and escalation planning. Understanding the evolving patient characteristics and their impact on outcome is essential to determine how best to do this, and to facilitate ongoing development and optimisation of acute NIV services.

Tab. 1. Demographics, clinical parameters and outcomes of pre-COVID and post-COVID acute NV cohorts. Showing mean ± standard deviation, or number of patients (percentage of patients). Statistical analysis performed with non-parametric tests, Chi-squared or Mann-Whitney U.

	Total (312)	Pre-Covid (171)	Post-Covid (141)	Significance
Age	68.9±0.7	68.0±11.5	70.0±12.0	0.128
Female, n (%)		103 (60.2)	82 (58.2)	0.710
Ceiling of care Full escalation NIV/HDU Ward based		 45 (26.3) 21 (12.3) 105 (61.4)	 23 (16.3) 2 (1.4) 116 (82.3)	<0.0001
Underlying Diagnosis COPD OHS NMD RLD CPE		 119 (69.6) 38 (22.2) 7 (4.1) 4 (2.3) 3 (1.8)	 95 (67.4) 31 (22) 4 (2.8) 8 (5.7) 3 (2.1)	0.610
CCI Score, median (IQR)	5 (3)	4 (3)	5 (3)	0.002

	Total (312)	Pre-Covid (171)	Post-Covid (141)	Significance
Outcomes				
NIV success		128 (74.9)	101 (71.6)	0.521
In-hospital mortality		38 (22.2)	37 (26.2)	0.408

COPD = Chronic Obstructive Pulmonary Disease; OHS = Obesity Hypoventilation Syndrome; NMD = Neuromuscular Disease; RLD = Restrictive Lung Disease; CPE = Cardiogenic Pulmonary Oedema; CCI = Charlson Comorbidity Index; NIV = Non-Invasive Ventilation; HDU = High Dependency Unit; IQR = Interquartile Range.

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Refractory Form of Chronic Idiopathic Demyelinating Polyneuropathy with Rituximab Effect: A Case Report

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ABSTRACT

The basic characteristic of chronic idiopathic demyelinating polyneuropathy (CIDP) is demyelination of peripheral nerves of autoimmune origin. Antibodies against various myelin sheath proteins play an important role in the pathogenesis of the disease. Cell-mediated immunity, characterised by T-cell and macrophage infiltration in peripheral nerves and spinal roots, is also significantly involved (1). Treatment of CIDP is aimed at suppressing inflammation, but also at removing autoantibodies, cytokines and other pro-inflammatory molecules from the blood. Treatment options include corticosteroids, (intravenous or subcutaneous) immunoglobulins, and plasma exchange (plasmapheresis). If a patient with CIDP does not show an adequate clinical response to these three treatment modalities, it is then refractory CIDP. Based on various studies, this affects up to 10% of patients.

We present here a patient with CIDP whose condition gradually stopped improving after all three commonly used treatment modalities (corticosteroids, immunoglobulins, and plasmapheresis). His neurological findings were very severe. The case was ultimately diagnosed as a refractory form of CIDP, which is discussed here in the light of current knowledge of this issue.

KEYWORDS

Chronic Inflammatory Demyelinating Polyradiculoneuropathy; Rituximab; autoimmune diseases; peripheral nervous system diseases; immunotherapy; plasma exchange

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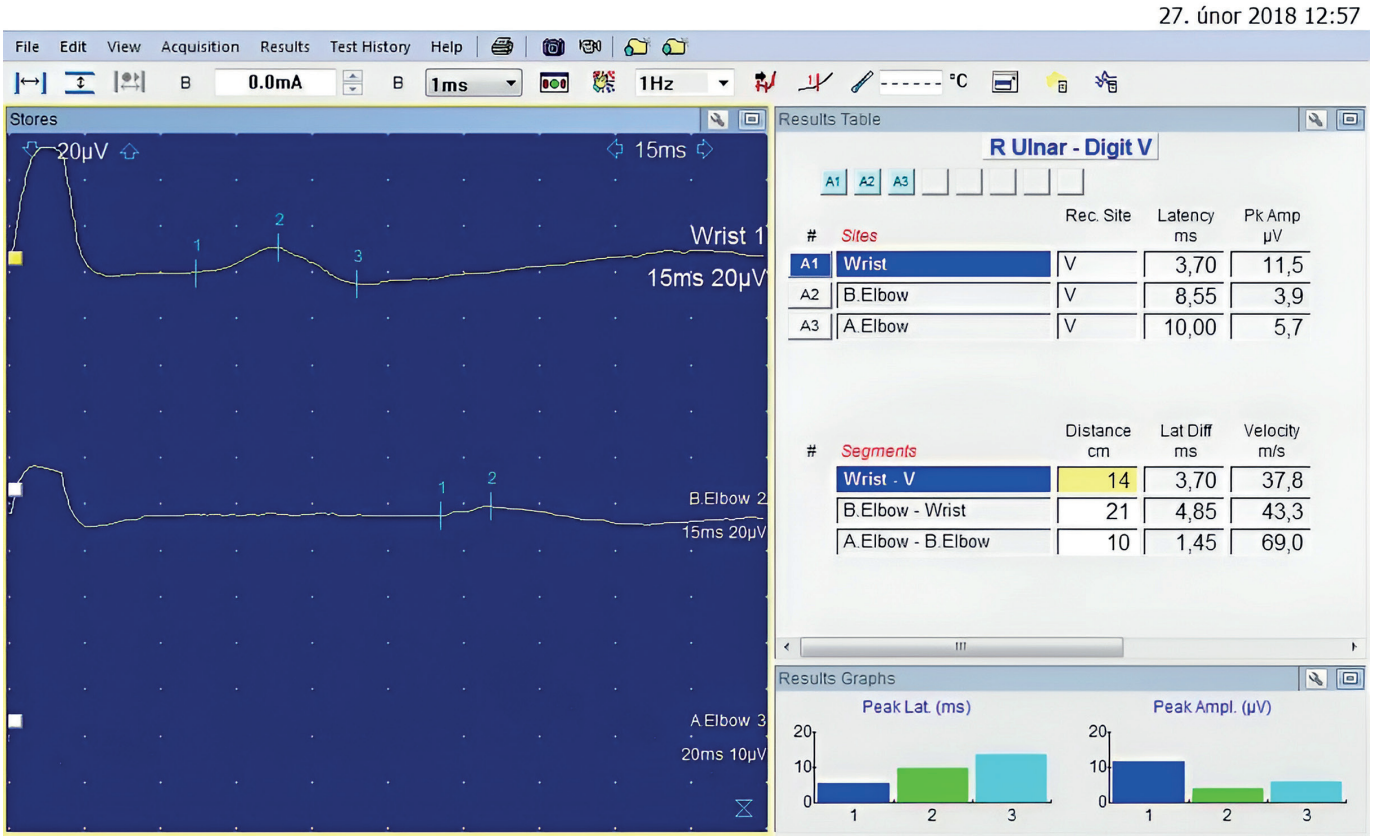
CASE REPORT

An active male, 184 cm tall, weighing 90 kg, born in 1979, was referred to the EMG laboratory in February 2018 with 5 months of progressive right hand motor impairment with loss of strength and sensory disturbance. The clinical findings included reduced finger duction, finger flexion (especially 4th–5th finger), weakening of lumbrical muscles in



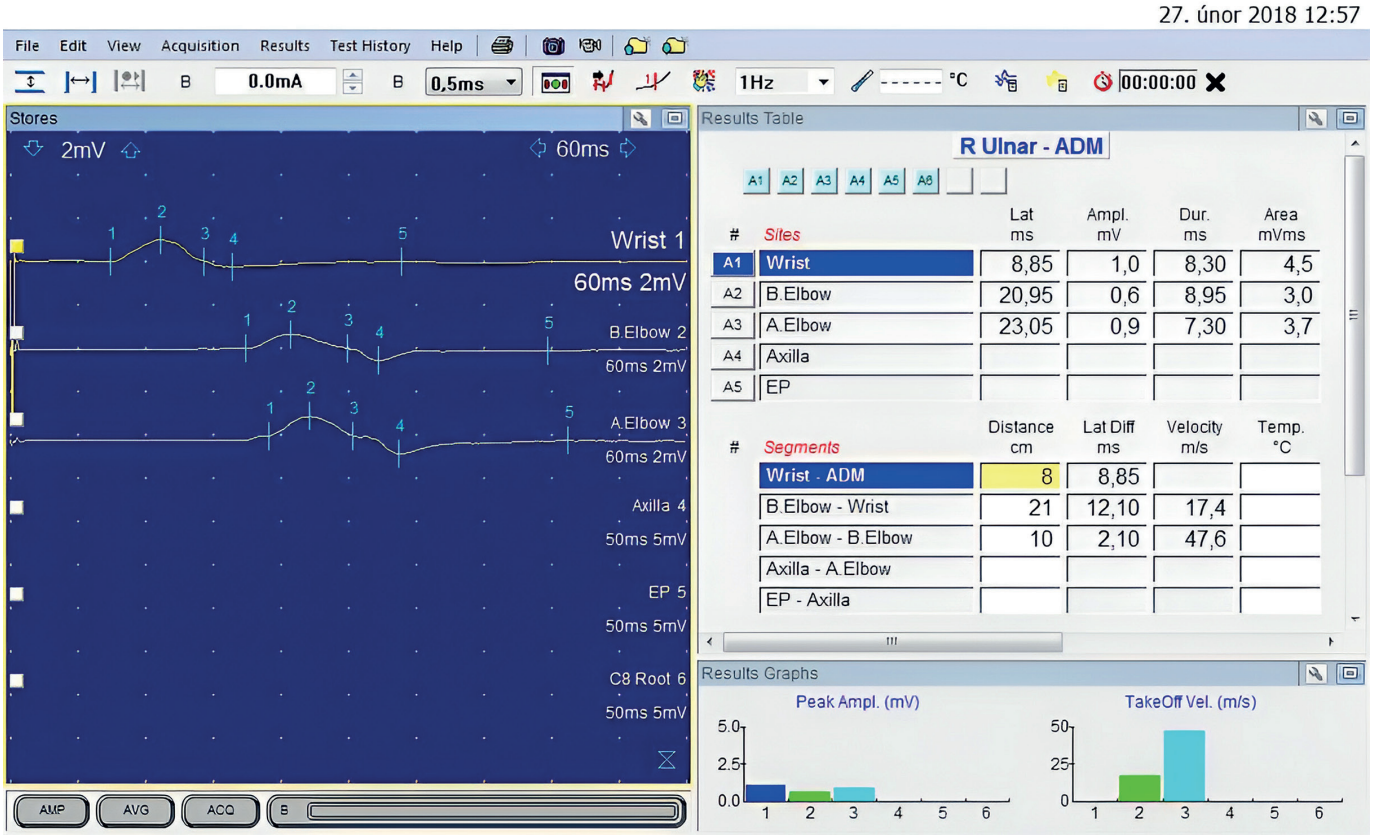


Fig. 1a, b R. ulnar nerve 27/02/2018.
Motor neurography – lesion of the distal part – DML 8.85 ms (3.8 upper limit of norm), duration of CMAP (8.00), A-CMAP 1.0 mV (6.0)m MCV in forearm 17.4 m/s (45.0).
Sensory neurography – longer distal sensory latency 3.70 ms (3.2), SCV 37.90 m/sw (45.0).

these fingers, and sensory disturbance in the hypothenar eminence, the 5th finger and half of the 4th finger. EMG revealed low CMAP following ulnar nerve stimulation (m. ADM, first dorsal interosseus) and slowed motor nerve conduction velocity in the proximal forearm Fig 1. Ultrasound examination showed no clear ulnar nerve

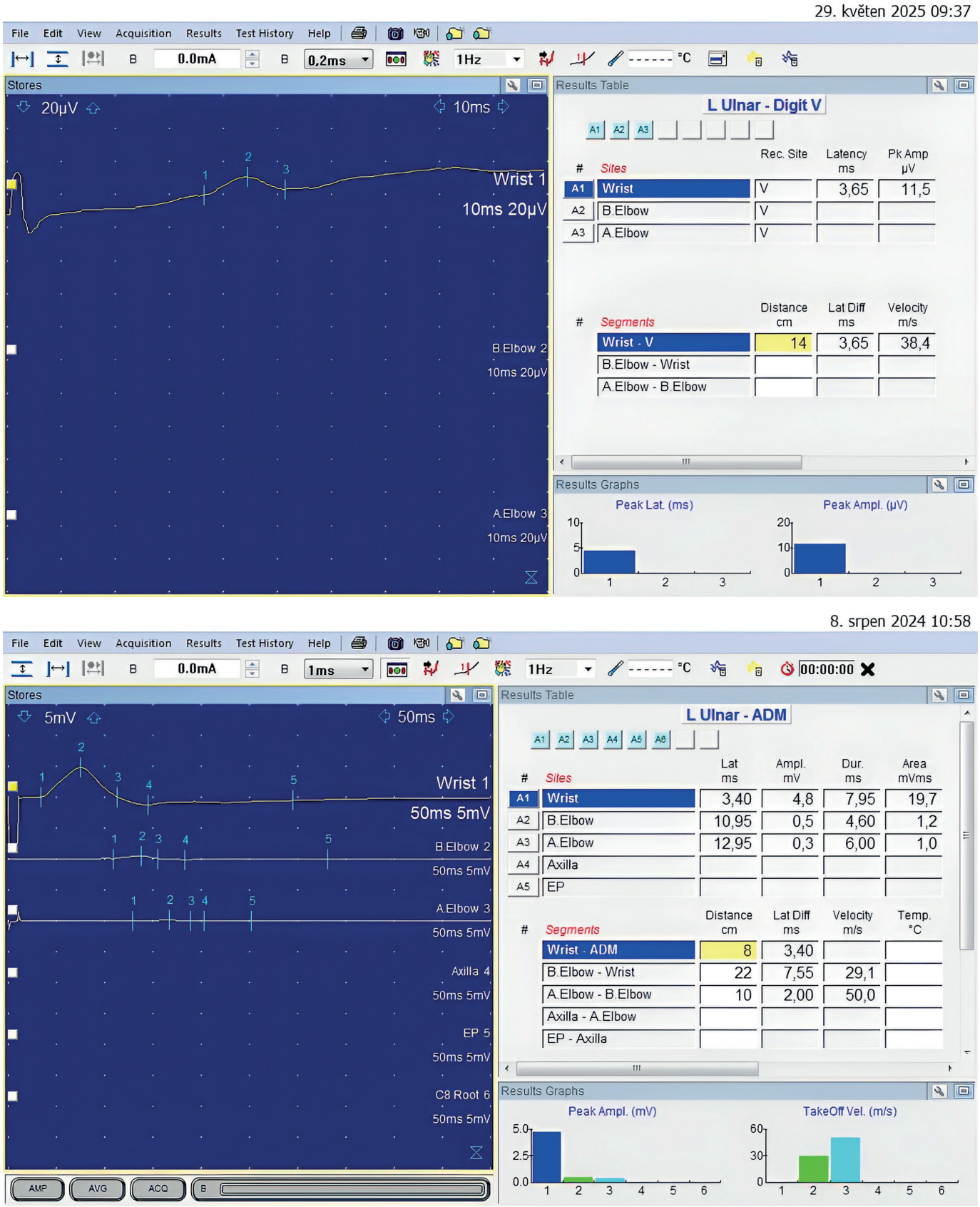


Fig. 2a, b L. ulnar nerve 08/08/2024.
Motor neurography – DML normal value, duration of CMAP 7.95 ms (borderline), A-CMAP 4.8 mV at wrist, 0.5 below the elbow, 0.3 above the elbow (6.0), MCV forearm 29.1 m/ and MCV ocress the elbow 50.00 (50).
Sensory neurography – SNAP latency 3.65 ms (3.80), SCV 38.4 m/s (45).

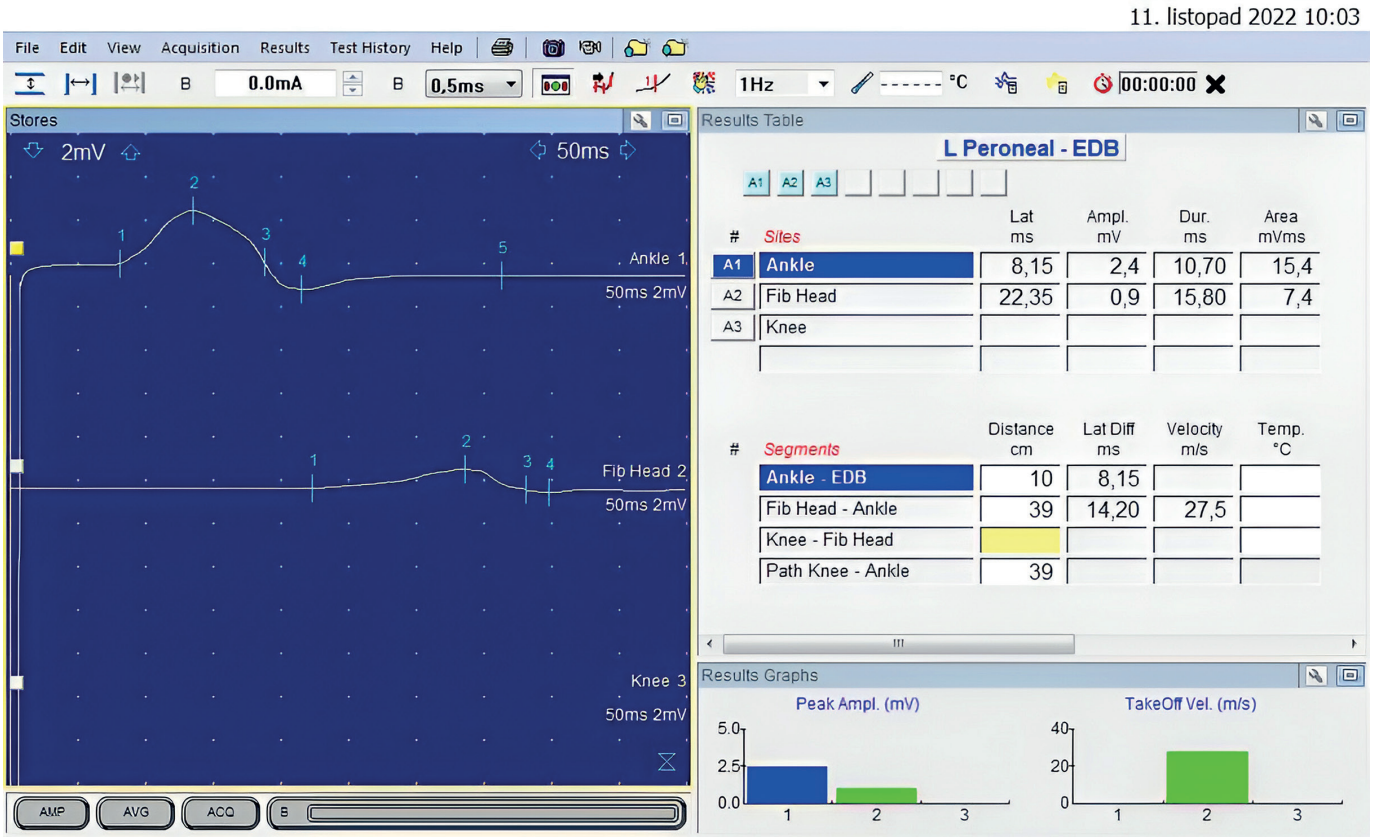


Fig. 3 L. peroneal nerve (extensor digitorum brevis muscle) 11/10/2022.
DML 8.15 ms (5.5), A-CMAP 2.4 and 0.9 mV (2.8), MCV 27.5 m/s (45).

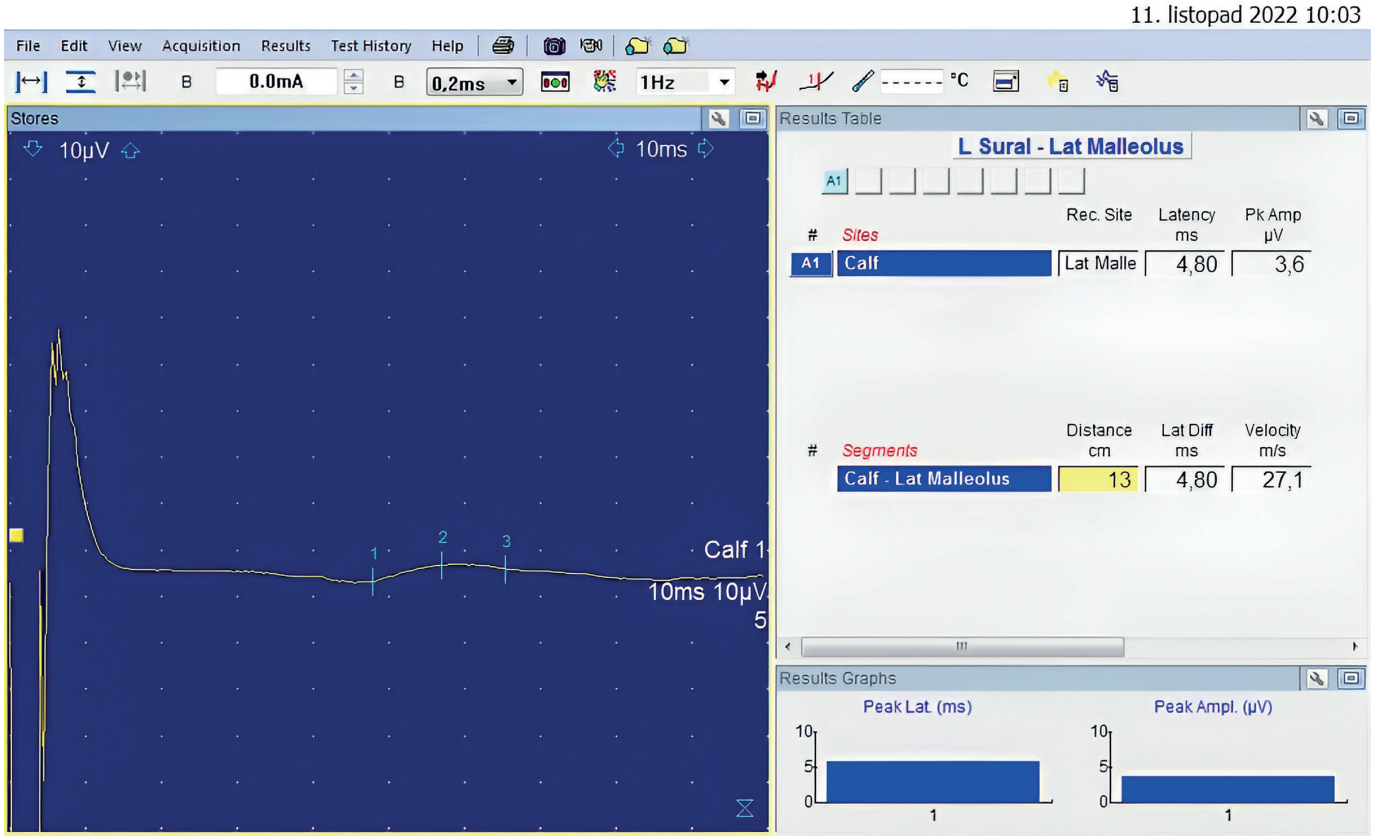


Fig. 4 L. sural nerve 11/02/2022.
SNAP latency 4.8 ms (4.0), A-SNAP 3.5 mV (8), SCV 27.1 m/s (45).

compression in the ulnar compartment. MRI of the ulnar nerve was recommended. On 25 April 2018, ulnar nerve surgery was performed at the elbow, after which there was a slight improvement lasting about 1 month, and then there was further progression, but the patient was not sent for EMG and no MRI was performed. In the spring of 2022, both motor function and sensation in the remaining fingers of the right hand deteriorated; in September 2022, gait and left-hand motor function were also affected. The control EMG from 31 October 2022 was suggestive of multifocal demyelinating disorder. CIDP, probably MADSAM (multifocal acquired demyelinating sensory and motor neuropathy, Lewis-Sumner syndrome) was suspected. Fig 2, Fig 3, Fig 4.

The samples were collected, including liquor (protein 0.8 g/l, glycorrhachia 3.44 mmol/l, 1 monocyte). IVIG therapy was started at a dose of 2 g/kg for 5 days. The patient's mobility improved and he was able to walk around his apartment with forearm crutches. Corticosteroid therapy was then initiated – prednisone 60 mg for 6 weeks with addition of cyclosporine 3×100 mg (Sandimmun). Nevertheless, the disease progressed and affected lower limb mobility so the patient had to use two forearm crutch. IVIG was re-administered at a dose of 70 g every 3 weeks, after which the findings stabilised. However, after the patient was switched to subcutaneous immunoglobulins, the pareses soon progressed, including gait and grip, with more marked deterioration on the left side. Since the autumn of 2023, there has been a steady progression of both paresis and atrophy. The patient then sat on the seat, could not stand up, had to be fed. The therapeutic effect of IVIG has waned gradually.

The laboratory findings identified only a fluctuating slight elevation of creatine kinase (CK) while antibodies against gangliosides were not detected. Cerebrospinal fluid was tested for IgG antibodies – against neurofascin-155, neurofascin-186, contactin, CASPR1 – which were not detected.

In August 2024, the patient was admitted to the neurological ICU, where a total of plasmapheresis (7 cycles) were performed. His condition did not improve, but no further attacks have occurred. He was then hospitalised for rehabilitation. Two weeks after plasmapheresis, IVIG was administered and after 4 days, the mobility of lower limbs and upper limb fingers slightly improved.

The patient has been treated with rituximab since 11 April 2025. At the follow-up in August 2025, no further attack was reported, and he was able to walk around his apartment with assistance and one forearm crutch. He was able to eat with a spoon in his right hand. Subjective sensory disturbances were less pronounced. He takes prednisone 20 mg daily, and cyclosporine 2×100 mg (Sandimmun). He continues with rituximab therapy at a dose of 1 g at first day, after 14 days another 1 g and then 1 g every 6 months. He performs rehabilitation exercises daily, both independently and with assistance from his family, and twice weekly at home under the supervision of a physiotherapist.

DISCUSSION

Recent diagnostic and therapeutic criteria (van den Bergh, 2021) define various forms of CIDP with the development of symmetric polyradiculoneuropathy during the course of the disease (2). There is also a treatment-refractory form (corticosteroids, immunoglobulins, and plasmapheresis), which affects 6–15% (3) of patients and is a serious and intractable issue. In a cohort of 45 patients (USA, Oregon), 11 people (24%) were refractory to first-line therapy. Seven out of 11 patients (64%) responded favourably to alternative treatment – rituximab or cyclophosphamide (4). Risk factors for refractory CIDP include multifocal form of CIDP, insidious onset, progressive course, and concomitant CNS involvement. According to various authors, initial corticosteroid therapy is successful in 68%. IVIG has an effect in 63–78% and plasmapheresis in 42–56% (5).

Our patient started with a lesion of the ulnar nerve on the right side when the neurosurgeon performed surgery in the elbow with little and short-term effect. The requirement for follow-up MRI examination of the ulnar nerve was not met. After 3 years, the patient experienced a significant deterioration in the right upper limb (n. ulnaris and n. medianus) but also had a significant nerve lesion in the left upper limb (unable to eat with his left hand) and in both lower limbs (only able to sit on a seat). This significantly delayed the diagnosis of CIDP, a multifocal variant of the MADSAM type.

Despite the initial good effect of immunomodulatory treatment, the therapeutic effect of immunoglobulins, corticosteroids and immunosuppressants gradually waned. At that time, plasmapheresis (7 cycles) was indicated, followed by 2 weeks of waiting for the immune system to stabilise. Only then did IVIG administration prove effective. Plasmapheresis has a substantially broader therapeutic effect than IVIG. Rituximab was administered in addition to the current therapy. His condition stabilised, sensitivity slightly improved with no further attacks.

It is important to accurately establish this diagnosis for the treatment strategy in the refractory form of CIDP. A large proportion of patients referred with a diagnosis of CIDP to a tertiary centre have another diagnosis (up to 40–60%) (5, 6). Such diseases do not improve with treatment. For example, the myelin sheath damage in nodopathies is not complement-dependent and patients do not respond to immunoglobulins (7).

Refractory forms of CIDP are not rare. Despite long-term administration of IVIG, the indication of plasmapheresis is necessary. Unlike IVIG, plasmapheresis removes autoantigens, cytokines and other pro-inflammatory substances (8). Then the therapeutic effect of IVIG and plasmapheresis is more likely.

In our patient, decompression of the ulnar nerve on the right side was performed hastily and without regard to the neurologist's request. The effect of the surgery was small and short-lived. Consequently, there was a significant delay in establishing a correct diagnosis and, in particular, in initiating effective therapy. After prolonged latency, multifocal polyneuropathy began to develop. Initially, treatment with intravenous immunoglobulins was moderately successful. Gradually, the effect of immunotherapy completely disappeared. The patient was bedridden, with near-plegic distal upper limbs. At that time, plasmapheresis (7 cycles) was indicated, followed by 2 weeks of waiting for the immune system to stabilise. Only then did the administration of IVIG have an effect. After slight improvement,

the patient is now stable on a regular dose of rituximab, prednisone 20 mg and cyclosporine 2×100 mg.

Treatment escalation and azathioprine, mycophenolate mofetil, and cyclosporine are used for the treatment of refractory form of CIDP while cyclophosphamide can be attempted for severe forms (Nascimento, 2025). Rituximab is a chimeric monoclonal antibody (IgG1) targeted against CD20, a surface antigen expressed on B lymphocytes responsible for pathological antibody production. The fact that CD20 is not expressed on stem cells or plasma cells makes rituximab a relatively safe medication, without a substantial risk of bone marrow suppression or impairment of long-term immunity. Various adverse events may occur after rituximab administration. The most common side effects include fever, bronchospasm, exanthema, angioedema, and hypotension. Rituximab is effective in approximately 50% of refractory CIDP cases, especially when associated with another autoimmune disorder (9).

Another group of modern medications consists of inhibitors targeting individual components of the complement system (eculizumab, ravulizumab, zilucoplan, riliprubart). By blocking complement activation, inflammatory changes in the myelin sheath do not develop, and demyelination is prevented (10).

Another group of modern therapies currently used in autoimmune neurological disorders includes neonatal Fc receptor (FcRn) blockers. Neonatal Fc receptors prolong the half-life of IgG and protect immunoglobulins from lysosomal degradation. Efgartigimod is an example of this therapeutic class (11).

Medicines to manage refractory CIDP should be taken for at least 3 months before switching to the next type of therapy.

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