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# Adverse events reporting of edaravone: a real-world analysis from FAERS database

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**For individuals with amyotrophic lateral sclerosis (ALS), intravenous edaravone is approved as a disease-modifying medication; yet, there have been many reports of adverse events (AEs). We examined the AEs associated with edaravone in this study using actual data from the FDA's (Food and Drug Administration) adverse event reporting system (FAERS). By extracting large-scale data from the FAERS database, this study used the signals of edaravone-associated AEs were quantified using the multiitem gamma Poisson shrinker (MGPS) method based on disproportionality, the Bayesian confidence propagation neural network (BCPNN), the reporting odds ratio (ROR), and the proportional reporting ratio (PRR). In the FAERS database, this study extracted data between April 2017 and March 2024, and edaravone was identified as the "primary suspect (PS)" in 2,986 AE reports. AEs associated with edaravone specifically targeted 27 system organ types (SOCs). Unexpectedly serious AEs that weren't mentioned in the drug insert, include abnormal hepatic function, catheter site thrombosis, pain, cerebral hemorrhage, infection, cerebral infarction, poor venous access, disseminated intravascular coagulation, vein collapse and cerebral venous sinus thrombosis. Our research found possible signals of new AEs that may offer substantial backing for clinical surveillance and edaravone risk assessment, but further research and validation are needed, especially for those AE that may occur in actual usage scenarios but are not yet explicitly described in the instruction.**

**Keywords** Edaravone, Real-world data analysis, Adverse events, Pharmacovigilance, Disproportionality analysis

Lou Gehrig's disease, often known as amyotrophic lateral sclerosis (ALS), is a neurological condition marked by the loss of motor neurons in the brain and spinal cord. Its primary symptoms, amyotrophy and muscle weakening, cause paralysis and ultimately death[1,2]. Since ALS is an adult-onset disease, patients' families and society as a whole bear a heavy weight due to the disease's 3–5 year median survival period after symptoms begin[3].

Its cause is unknown, however, 90% of cases are assumed to be sporadic (SALS), while 10% may be familial (FALS)[4]. While the exact pathophysiological pathways and environmental factors influencing the disease remain unknown, the available data indicates that free radicals are a major contributor to the advancement of ALS[5,6]. Because of its poor capacity for regeneration and its limited capacity to scavenge free radicals, free radicals can damage the central nervous system (CNS)[7].

Edaravone, a scavenger targeting peroxynitrite and lipid peroxy free radicals, can effectively diminish the level of 3-nitrotyrosine in the cerebrospinal fluid of patients diagnosed with ALS, thereby mitigating the progression of ALS[8,9]. In 2017, the FDA authorized it as a therapy for ALS[10]. The product manual states that contusion, gait disruption, and headache are the most frequent adverse events (AEs), affecting at least 10% of patients treated with edaravone injection and happening more frequently than with placebo. Adverse responses related to skin and subcutaneous tissue diseases, including hypersensitivity and allergic reactions, have been observed in post-marketing experience with edaravone. To effectively counsel patients on therapy, it is crucial to continuously monitor and evaluate the safety of drugs.

A major source of information for studies on pharmacological adverse events is the FDA's (Food and Drug Administration) adverse event reporting system (FAERS), a database that houses multiple reports pertaining to drug AEs[11,12]. The present study endeavors to conduct a thorough analysis of edaravone's AEs signals by

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utilizing the FAERS database and implementing diverse signal quantification approaches. This will provide further empirical evidence to enhance clinical decision-making.

## Data sources and methods

### Data sources

The FAERS database, which is updated quarterly by the FDA, was the source of data for a retrospective observational pharmacovigilance study. The FAERS database was consulted in our study in order to collect AE reports connected to edaravone that were filed between April 2017 and March 2024, as the primary suspected (PS) drug. After that, the data were imported into Excel and Python 3.10.0 for cleaning and analysis.

### Data processing

We extracted 11,953,750 reports using the FDA-recommended procedure for getting rid of duplicate complaints from the FAERS database. From the DEMO table, we chose the variables PRIMARYID, CASEID, and FDA_DT. We then sorted the data according to CASEID, FDA_DT, and PRIMARYID. For cases with the same CASEID, the report with the highest FDA_DT value was kept. We then retained the report with the highest PRIMARYID value for cases that had the same CASEID and FDA_DT. Reports were removed following data deduplication on the basis of the CASEID found in the deleted report list. Lastly, 10,214,975 records were included for additional examination (Fig. 1). The system organ class (SOC) and preferred terms (PTs) were then obtained by using MedDRA26.0 to rectify PT names in the FAERS database.

### Statistical analysis

We used the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS) algorithms to examine the relationships between the drug and the listed AEs, based on the principles of disproportionality analysis and Bayesian analysis. Table 1 lists the equations and requirements for each of the four algorithms.

## Results

### General characteristics

11,953,755 cases total—all reported cases from Q2 2017 to Q1 2024—were collected from the FAERS database. Following screening and the removal of duplicates, 2,986 reports of adverse reactions to edaravone were found. After the reported data were analyzed in this study, Table 2 lists the general characteristics of the related AEs. Males made up 59.26% of reported AEs, compared to females' 40.74%. In terms of age distribution, the age group of 18 to 65 years old had the highest percentage of AE (52.10%), followed by the age group of 65 and older (46.26%). The median age was 65 (interquartile range [IQR] 57–72). Furthermore, we found that riluzole (57.11%), phenylbutyrate (13.29%), baclofen (7.76%), aspirin (7.63%), and gabapentin (4.74%) are frequently used co-administered medications that may result in potential AEs. Notably, rather than being from medical experts, consumers provided the majority (63.71%) of the reports. The United States (84.40%) was the highest

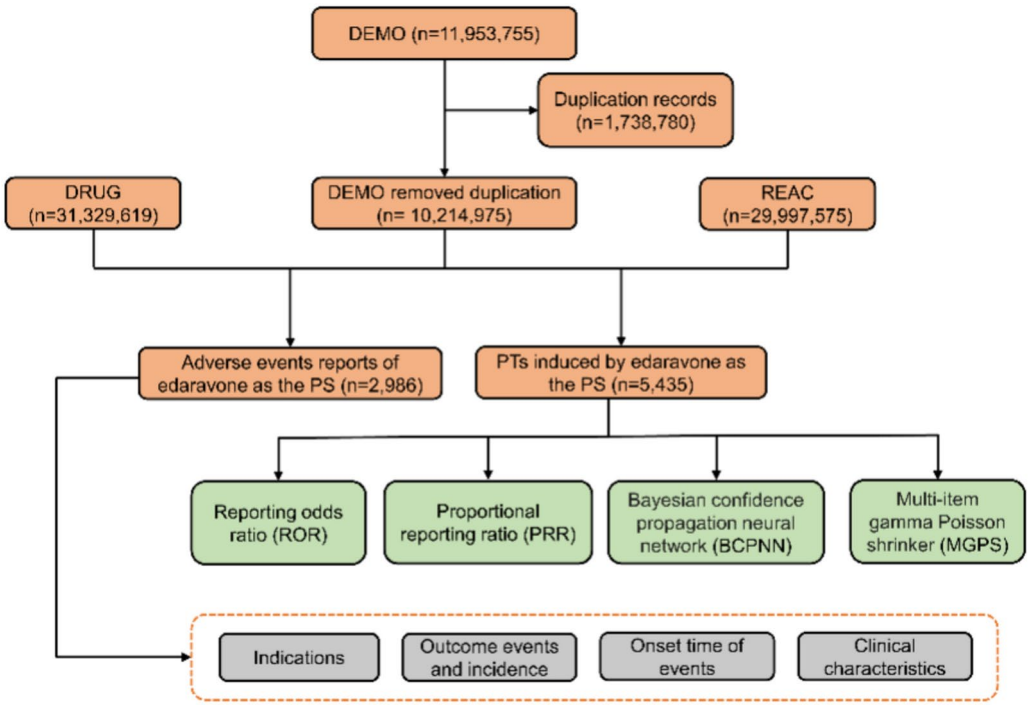


**Fig. 1**. The flow diagram of selecting edaravone-related AEs from FAERS database.

| Algorithms | Indicator | Equation | Criteria |
|---|---|---|---|
| ROR | ROR | ROR = ad/cb | ROR05 > 1, N ≥ 2 |
| | | $95CI = e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)\wedge0.5}$ | |
| PRR | PRR | PRR = [a/(a + b)]/[c/(c + d)] | PRR ≥ 2 |
| | $\chi2$ | $\chi2 = [(ad\text{-}bc)^2 (a+b+c+d)]/[(a+b)(c+d)(a+c)(b+d)]$ | $\chi2 \geq 4$, N ≥ 3 |
| BCPNN | IC | IC = log2 [a (a + b + c + d)]/[(a + c)(a + b)] | IC025 > 0 |
| | | $95CI = e^{\ln(IC)\pm1.96(1/a+1/b+1/c+1/d)\wedge0.5}$ | |
| MGPS | EBGM | EBGM = a (a + b + c + d)/(a + c)/(a + b) | EBGM05 > 2, N ≥ 0 |
| | | $95CI = e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)\wedge0.5}$ | |

**Table 1**. Summary of major algorithms used for signal detection. N, number of adverse event reports; CI, confidence interval; ROR, reporting odds ratio; ROR05, the lower limit of the 95 two-sided CI of the ROR; N, the number of co-occurrences; PRR, proportional reporting ratio; $\chi^2$, chi-squared; BCPNN, bayesian confidence propagation neural network; IC, information component; IC025, the lower limit of the 95 two-sided CI of the IC; MGPS, multi-item gamma Poisson shrinker; EBGM, empirical bayesian geometric mean; EBGM05, the lower 95 two-sided CI of EBGM.

reporting nation, followed by Japan (9.34%) and China (1.41%). Death (57.60%) was the most significant AE result, followed by hospitalization (25.66%), conditions posing a threat to life (1.46%), and disability (0.98%).

## Signal detection

The edaravone signal intensity at the SOC level is shown in Table 3. The data show that edaravone-induced AEs targeted 27 organ systems. Significant SOCs that met the criteria of four incidents at once were general disorders and administration site conditions (SOC: 10,018,065, n = 1,737). The 68 significantly disproportionate PTs that concurrently complied with all four algorithms are listed in Table 4, where they were arranged in decreasing order of ROR values. The top five edaravone PTs in terms of number of cases were asthenia (n = 135), gait disturbance (n = 99), therapeutic response unexpected (n = 98), respiratory failure (n = 40), and Respiratory disorder (n = 29). The top five PTs in terms of significance were Catheter site thrombosis (ROR = 149.27), Gastric fistula (ROR = 93.20), Catheter site swelling (ROR = 65.28), Vein collapse (ROR = 43.31), and Catheter site infection (ROR = 28.50). Notably, several unexpectedly significant AEs were identified that were not noted in the labeling, including abnormal hepatic function, catheter site thrombosis, pain, cerebral hemorrhage, infection, cerebral infarction, poor venous access, disseminated intravascular coagulation, vein collapse and cerebral venous sinus thrombosis. Table 4 provides other unexpected PTs.

## AE onset time

The database was searched for the onset times of AEs associated with edaravone. After excluding patients whose time-to-onset analysis report fields in FAERS were empty or contained false information, 303 AEs (10.15%) with a median start time of 16 days were observed. AEs occurred within the first month following the start of edaravone in about 56.11% of patients (n = 170) (Fig. 2). Furthermore, the percentage of patients with AEs occurring after two months (n = 23, 7.59%) and three months (n = 31, 10.23%) was considerably lower than the total number of AEs in the first month.

## Discussion

Preclinical and clinical trials often provide the majority of evidence regarding the safety and efficacy of drugs[13]. However, it can be difficult to fully understand how medications affect people in the real world, especially in terms of safety, due to things like trial design and small sample sizes. For the purpose of assessing drug safety and striking a balance between benefits and risks in clinical decision-making, it is imperative that attention be paid to risk signals of adverse drug effects in clinical applications. In this work, we gathered and used a large sample of real-world data from FEARS to evaluate the safety of edaravone through pharmacovigilance. The purpose is to offer a resource for clinical practice on pharmaceutical safety.

From Q2 2017 to Q1 2024, 2,986 edaravone-related AEs reports overall, originating from various nations and areas worldwide, were gathered from the FAERS database. In the situations where edaravone-related AEs were documented, males accounted for a higher proportion (59.26%) than females (40.74%). Research has indicated that female hormones, including progesterone and estrogen, may provide some defense against ALS causes[14], perhaps contributing to higher rate of ALS in the male population[15]. Subsequently, the use of edaravone in the male population increased, which in turn led to a bigger patient cohort of males in our study. In addition, a greater percentage of AEs had a median age of 65. This is likely due to the fact that the incidence of ALS increases with age, peaking between 60 and 79 years of age[16,17]. Consequently, we must advocate for close surveillance of adverse events in older male patients. Since AEs can be potentially fatal or accelerate the course of a disease, it is imperative that they be identified as soon as possible.

It is noteworthy that consumers, as opposed to medical experts, filed the majority of AE reports (63.71%). This could suggest that people are more likely to report side effects right away after taking an edaravone intra, or it may indicate that medical professionals have a greater supervisory rather than reporting role in the treatment process. Given that 84.40% of the reports come from the United States, reporting patterns in particular areas or

| Characteristics | Edaravone-induced AE reports (n = 2,986) | | |
|---|---|---|---|
| Number of events | Available number, n | Case number, n | Case proportion, % |
| Gender, n (%) | 2062 | – | 69.06% |
| Female | – | 840 | 40.74% |
| Male | – | 1222 | 59.26% |
| Age (years), n (%) | 856 | – | 28.67% |
| < 18 | – | 14 | 1.64% |
| 18 ≤ and ≤ 65 | – | 446 | 52.10% |
| > 65 | – | 396 | 46.26% |
| Median (IQR) | – | 65 (57–72) | - |
| Weight (Kg), n (%) | 193 | – | 6.46% |
| < 80 | – | 138 | 71.50% |
| 80 ≤ and ≤ 100 | – | 36 | 18.65% |
| > 100 | – | 19 | 9.84% |
| Median (IQR) | – | 70 (59.47–81.27) | - |
| Reported countries, n (%) | 2975 | – | 99.63% |
| US | | 2511 | 84.40% |
| JP | | 278 | 9.34% |
| CN | | 42 | 1.41% |
| Other country | – | 144 | 4.84% |
| Indications, n (%) | 2206 | – | 73.88% |
| Amyotrophic lateral sclerosis | – | 2088 | 94.65% |
| Combination drugs, n (%) | 760 | - | 25.45% |
| Riluzole | – | 434 | 57.11% |
| Phenylbutyrate/taurursodiol | – | 101 | 13.29% |
| Baclofen | – | 59 | 7.76% |
| Aspirin | – | 58 | 7.63% |
| Gabapentin | – | 36 | 4.74% |
| Outcomes, n (%) | 2986 | – | 100.00% |
| Non-serious Outcome | – | 1552 | 51.98% |
| Serious Outcome | – | 1434 | 48.02% |
| Death | – | 826 | 57.60% |
| Life-threatening | – | 21 | 1.46% |
| Hospitalization | – | 368 | 25.66% |
| Disability | – | 14 | 0.98% |
| Other serious outcomes | – | 392 | 27.34% |
| Time-to-onset (days) | 303 | | 10.15% |
| Median (IQR) | | 16 (3–99) | |
| Reporters, n (%) | 2984 | – | 99.93% |
| Health professional | – | 1083 | 36.29% |
| Consumer | – | 1901 | 63.71% |
| Reporting year, n (%) | 2986 | – | 100.00% |
| 2024Q1 | – | 167 | 5.59% |
| 2023 | – | 441 | 14.77% |
| 2022 | – | 365 | 12.22% |
| 2021 | – | 322 | 10.78% |
| 2020 | – | 479 | 16.04% |
| 2019 | – | 531 | 17.78% |
| 2018 | – | 585 | 19.59% |
| 2017Q2-Q4 | – | 96 | 3.22% |

**Table 2**. Features of reports associated with edaravone.

cultures may also be reflected in this. In order to confirm any potential regional or cultural biases, more research is required on this subject.

ALS is an adult-onset, incurable motor neuron disease. While several medications are widely accessible internationally, such as riluzole, edaravone, and sodium phenylbutyrate-taurursodiol, their advantages are limited, while other treatments only treat symptoms[18]. Strong opioids and several muscle relaxants have been

| System Organ Class (SOC) | Edaravone Cases Reporting SOC | ROR (95% two-sided CI) | PRR (χ2) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|
| General disorders and administration site conditions | 1737 | 2.96 (2.79–3.14)[a] | 2.20 (1384.05)[a] | 1.14 (1.07)[a] | 2.20 (2.07)[a] |
| Nervous system disorders | 582 | 1.88 (1.72–2.05)[a] | 1.77 (208.80) | 0.82 (0.75)[a] | 1.77 (1.62) |
| Respiratory, thoracic and mediastinal disorders | 307 | 1.64 (1.46–1.84)[a] | 1.60 (71.90) | 0.68 (0.60)[a] | 1.60 (1.42) |
| Surgical and medical procedures | 116 | 1.46 (1.21–1.76)[a] | 1.45 (16.39) | 0.53 (0.44)[a] | 1.45 (1.20) |
| Musculoskeletal and connective tissue disorders | 229 | 1.17 (1.02–1.34)[a] | 1.16 (5.34) | 0.22 (0.19)[a] | 1.16 (1.02) |
| Infections and infestations | 201 | 0.79 (0.69–0.91) | 0.80 (10.81) | -0.32 (-0.37) | 0.80 (0.69) |
| Vascular disorders | 81 | 0.75 (0.61–0.94) | 0.76 (6.35) | -0.40 (-0.50) | 0.76 (0.61) |
| Hepatobiliary disorders | 32 | 0.74 (0.52–1.05) | 0.74 (2.83) | -0.43 (-0.60) | 0.74 (0.53) |
| Gastrointestinal disorders | 228 | 0.71 (0.62–0.81) | 0.72 (25.80) | -0.47 (-0.53) | 0.72 (0.63) |
| Cardiac disorders | 63 | 0.62 (0.48–0.79) | 0.62 (14.56) | -0.68 (-0.87) | 0.62 (0.49) |
| Investigations | 154 | 0.61 (0.52–0.72) | 0.63 (36.20) | -0.67 (-0.79) | 0.63 (0.53) |
| Product issues | 54 | 0.56 (0.43–0.74) | 0.57 (18.00) | -0.81 (-1.06) | 0.57 (0.44) |
| Metabolism and nutrition disorders | 54 | 0.51 (0.39–0.66) | 0.51 (25.41) | -0.96 (-1.26) | 0.51 (0.39) |
| Injury, poisoning and procedural complications | 299 | 0.50 (0.45–0.57) | 0.54 (136.15) | -0.90 (-1.01) | 0.54 (0.48) |
| Skin and subcutaneous tissue disorders | 122 | 0.49 (0.41–0.59) | 0.51 (61.30) | -0.98 (-1.17) | 0.51 (0.42) |
| Social circumstances | 11 | 0.42 (0.23–0.75) | 0.42 (8.94) | -1.26 (-2.27) | 0.42 (0.23) |
| Immune system disorders | 28 | 0.38 (0.26–0.55) | 0.39 (27.73) | -1.37 (-1.99) | 0.39 (0.27) |
| Psychiatric disorders | 83 | 0.38 (0.30–0.47) | 0.39 (83.39) | -1.36 (-1.69) | 0.39 (0.31) |
| Ear and labyrinth disorders | 8 | 0.34 (0.17–0.67) | 0.34 (10.50) | -1.57 (-3.14) | 0.34 (0.17) |
| Blood and lymphatic system disorders | 22 | 0.26 (0.17–0.39) | 0.26 (46.41) | -1.93 (-2.93) | 0.26 (0.17) |
| Eye disorders | 14 | 0.17 (0.10–0.28) | 0.17 (57.69) | -2.55 (-4.32) | 0.17 (0.10) |
| Congenital, familial and genetic disorders | 2 | 0.16 (0.04–0.65) | 0.16 (8.57) | -2.61 (-10.45) | 0.16 (0.04) |
| Endocrine disorders | 2 | 0.13 (0.03-0.54) | 0.13 (11.18) | -2.89 (-11.58) | 0.13 (0.03) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 16 | 0.09 (0.05-0.15) | 0.09 (148.29) | -3.44 (-5.61) | 0.09 (0.06) |
| Reproductive system and breast disorders | 2 | 0.06 (0.01-0.22) | 0.06 (31.65) | -4.14 (-16.56) | 0.06 (0.01) |
| Pregnancy, puerperium and perinatal conditions | 1 | 0.05 (0.01–0.38) | 0.05 (16.65) | − 4.21 (− 29.91) | 0.05 (0.01) |

**Table 3**. Signal values of reports associated with edaravone at the SOC level. SOC, system organ class; FAERS, the FDA Adverse Event Reporting System; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; χ2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM. [a] Indicates statistically significant potential signals in algorithm.

approved by the Japanese government for the treatment of respiratory distress, pain, and stiffness in individuals with ALS[19]. We found that in the analyses published for combination medicines, riluzole had the highest percentage of reported data. Given that the FDA has only approved two drugs to treat ALS at this time—edaravone and riluzole—this may be the case[20]. The most frequent adverse effects of riluzole are weakness, nausea, and a brief rise of liver enzyme levels[21]. Therefore, further clinical studies are needed on whether riluzole exacerbates the occurrence of edaravone AEs. We present a median time to commencement AEs of 16 days following edaravone initiation, with the majority of cases (n = 170, 56.11%) happening during the first month. After medication, throughout the first month, before progressively stabilizing. These findings imply that, in order to maximize patient safety, particular attention should be given to edaravone-associated adverse events during the first month of treatment.

Disproportionation analysis revealed that administration site problems and general abnormalities were the most prevalent and significant signals at the SOC level. It was determined that gait disturbance and incapacity were common AEs associated with edaravone inhibitors. Three randomised, placebo-controlled clinical trials report that dermatitis contact, gait disturbance, and contusion were AEs that occurred at ≥ 2% incidence in the edaravone group compared to the placebo group. These findings align with our findings[22].

Notably, our analysis discovered 14 novel and unanticipated AEs that were not included in the FDA labels. These included abnormal hepatic function, catheter site thrombosis, pain, cerebral hemorrhage, infection, cerebral infarction, poor venous access, disseminated intravascular coagulation, vein collapse, and cerebral venous sinus thrombosis. Given that patients with ALS frequently present cardiovascular risk factors and often experience cerebrovascular disease accompanied by pathological changes in their cerebellar vessels, it is noteworthy that ALS patients exhibit reduced levels of vascular endothelial growth factor, which compromises the formation of endothelial cells and the integrity of the blood–brain barrier[23]. Consequently, it is highly plausible to attribute the adverse event caused by edaravone-induced vascular damage to disease progression. The results of a multicenter propensity score-matched cohort study revealed potential treatment-related adverse reactions, including elevated transaminases (n = 1), intracranial hemorrhage when combined with oral anticoagulants (n = 1), port infections (n = 5), thrombophlebitis (n = 1), and seven cases of infusion port problems attributed to infection[24]. In another analysis, three serious hepatic events (one case of elevated liver enzymes, one liver

| SOC | Preferred Terms (PTs) | Edaravone Cases Reporting PT | ROR (95% two-sided CI) | PRR (χ2) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Nervous system disorders | Amyotrophic lateral sclerosis | 103 | 745.57 (606.00–917.28) | 731.46 (66,342.05) | 9.34 (7.59) | 645.96 (525.04) |
| Respiratory, thoracic and mediastinal disorders | Dependence on respirator | 7 | 155.32 (73.25–329.35) | 155.12 (1042.59) | 7.24 (3.41) | 150.91 (71.17) |
| Surgical and medical procedures | Tracheostomy | 16 | 149.32 (90.81–245.51) | 148.88 (2288.50) | 7.18 (4.37) | 145.00 (88.18) |
| General disorders and administration site conditions | Catheter site thrombosis* | 5 | 149.27 (61.38–363.02) | 149.13 (716.34) | 7.18 (2.95) | 145.23 (59.72) |
| Surgical and medical procedures | Gastrostomy | 16 | 122.64 (74.67–201.41) | 122.28 (1882.93) | 6.90 (4.20) | 119.65 (72.85) |
| Social circumstances | Feeding tube user | 4 | 97.73 (36.35–262.76) | 97.66 (376.04) | 6.58 (2.45) | 95.98 (35.70) |
| Injury, poisoning and procedural complications | Discontinued product administered | 4 | 96.88 (36.04–260.43) | 96.80 (372.73) | 6.57 (2.44) | 95.15 (35.40) |
| Gastrointestinal disorders | Gastric fistula | 4 | 93.20 (34.68–250.46) | 93.13 (358.51) | 6.52 (2.43) | 91.60 (34.08) |
| Surgical and medical procedures | Mechanical ventilation | 11 | 86.15 (47.46–156.36) | 85.97 (909.68) | 6.40 (3.53) | 84.67 (46.65) |
| General disorders and administration site conditions | Catheter site swelling | 5 | 65.28 (27.02–157.72) | 65.22 (312.50) | 6.01 (2.49) | 64.47 (26.69) |
| Surgical and medical procedures | Gastrointestinal tube insertion | 10 | 56.93 (30.52–106.21) | 56.83 (542.87) | 5.81 (3.12) | 56.26 (30.16) |
| Investigations | Forced vital capacity decreased | 4 | 47.50 (17.75–127.14) | 47.47 (180.40) | 5.56 (2.08) | 47.07 (17.59) |
| Nervous system disorders | Muscle contractions involuntary | 11 | 45.25 (24.98–81.96) | 45.16 (471.18) | 5.49 (3.03) | 44.80 (24.74) |
| Vascular disorders | Vein collapse* | 4 | 43.31 (16.19–115.88) | 43.28 (163.92) | 5.42 (2.03) | 42.95 (16.05) |
| Nervous system disorders | Aphasia | 83 | 35.69 (28.72–44.37) | 35.16 (2738.78) | 5.13 (4.13) | 34.95 (28.12) |
| Surgical and medical procedures | Central venous catheterisation | 9 | 34.28 (17.79–66.05) | 34.23 (288.52) | 5.09 (2.64) | 34.02 (17.66) |
| Product issues | Device connection issue | 5 | 31.17 (12.94–75.10) | 31.14 (145.04) | 4.95 (2.06) | 30.97 (12.85) |
| Infections and infestations | Catheter site infection* | 7 | 28.50 (13.55–59.92) | 28.46 (184.55) | 4.82 (2.29) | 28.32 (13.47) |
| General disorders and administration site conditions | Disease progression | 274 | 28.18 (24.95–31.83) | 26.81 (6788.34) | 4.74 (4.19) | 26.69 (23.63) |
| General disorders and administration site conditions | Therapeutic response unexpected | 98 | 26.00 (21.28–31.76) | 25.55 (2302.42) | 4.67 (3.82) | 25.43 (20.82) |
| Infections and infestations | Injection site infection* | 6 | 25.71 (11.52–57.36) | 25.68 (141.69) | 4.68 (2.10) | 25.57 (11.46) |
| Nervous system disorders | Cerebral venous sinus thrombosis* | 3 | 24.46 (7.87–76.07) | 24.45 (67.18) | 4.61 (1.48) | 24.35 (7.83) |
| General disorders and administration site conditions | Infusion site rash | 3 | 24.32 (7.82–75.62) | 24.31 (66.75) | 4.60 (1.48) | 24.21 (7.78) |
| General disorders and administration site conditions | Catheter site pain* | 5 | 22.78 (9.46–54.86) | 22.76 (103.61) | 4.50 (1.87) | 22.67 (9.42) |
| Nervous system disorders | Speech disorder | 80 | 19.84 (15.90–24.75) | 19.56 (1404.84) | 4.28 (3.43) | 19.49 (15.63) |
| Surgical and medical procedures | Hospice care | 23 | 19.58 (12.99–29.52) | 19.50 (402.43) | 4.28 (2.84) | 19.44 (12.90) |
| Nervous system disorders | Dysgraphia | 10 | 18.05 (9.69–33.59) | 18.01 (160.19) | 4.17 (2.24) | 17.96 (9.65) |
| Product issues | Product leakage | 10 | 17.45 (9.37–32.48) | 17.42 (154.28) | 4.12 (2.21) | 17.37 (9.33) |
| Infections and infestations | Device related sepsis | 3 | 15.28 (4.92–47.46) | 15.27 (39.90) | 3.93 (1.26) | 15.23 (4.90) |

**Table 4**. Signal strength of edaravone reports at preferred term (PT) levels.

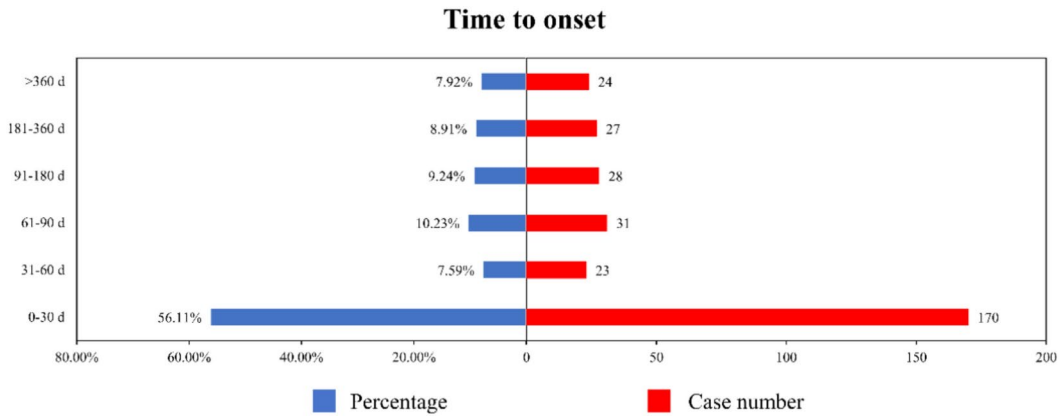


**Fig. 2**. Time to onset of reported AEs grouped by month.

disease, and one hepatomegaly) were identified along with 34 site infections in the safety data[25]. Furthermore, the impaired hepatic function may be associated with increased plasma concentrations of the prototype edaravone[26]. Thankfully, the maintenance dosing regimen for edaravone for the treatment of ALS comprises a ten-day medication period followed by a two-week discontinuation phase, which may act effectively as a washout period to prevent adverse events resulting from blood level accumulation[27]. Additionally, excessive dosage may potentially induce cerebral hemorrhage by augmenting blood flow to the cerebral vasculature, although this remains speculative. The majority of infusion-related issues were found to be associated with intravenous drug administration. Relevant attention should therefore be duly accorded to the practical implementation of clinical procedures.

Catheter site thrombosis has been reported comparatively infrequently, however it showed a strong signal strength, with ROR 149.27 (61.38–363.02), PRR 149.13 (716.34), IC 7.18 (2.95), and EBGM 145.23 (59.72), respectively. According to studies, each edaravone infusion also includes sodium hydroxide, phosphoric acid, 40 mg of sodium bisulfite, and 20 mg of L-cysteine, all of which are adjusted to a pH of 4. Even in small amounts, the first two are antioxidants on their own. Injection of sodium bisulfite into rabbit ear veins results in thrombosis. This pH of acidic solutions increases the risk of infusion thrombophlebitis[28]. A randomized controlled experiment revealed that heparin added to the infusion fluid decreased catheter-site thrombosis[29]. Additionally, it has been discovered that buffering the infusion solution to a pH of 7.4 can lessen this effect[30]. Additionally, it is advised that the infusion site be switched every 24 or 48 h in cases of extended intravenous therapy. Additionally, this reduces the chance of catheter-site thrombosis[31].

However, a number of frequent AEs that are indicated in the FDA label—like headache, eczema, glycosuria, and tinea infection—did not show up as meaningful signals in our data analysis. The widespread occurrence of AEs in all medications listed in the FAERS database provides an explanation for these phenomena. The large number of reports of AEs associated with different drugs may attenuate the signal scores. For a given medication, proportionation analysis necessitates a higher (or lower) frequency of AE reporting. Thus, the lack of signal in the imbalance analysis does not necessarily mean that adverse events are not present, but may be due to insufficient reporting frequency or other factors that fail to show a signal.

The study is not without its limits. First of all, because FAERS depends on voluntary reporting, there is a bias in reporting that may cause AEs to be underreported or underestimated, which would impair the data's accuracy. Since voluntary reporting of AEs is not restricted to healthcare professionals, consumers can also report AEs; yet, in some cases, reported AEs may exhibit a lack of professionalism. Second, it was not able to determine the actual incidence of each AE due to missing important information, incomplete data, and an inadequate total number of patients receiving edaravone. Population heterogeneity adds to the complexity, since research subjects come in a wide variety of ages, genders, races, and health statuses. It is also more difficult to identify and evaluate new safety signals in a timely manner when there are temporal delays and confounding factors present. In addition, signal scores may be weakened by the large number of adverse event reports associated with different drugs. For a particular drug, an unbalanced analysis would require a higher (or lower) frequency of adverse event reports, resulting in some common adverse events indicated in the FDA labeling (e.g., headache, eczema, diabetes, and ringworm infections) failing to show up as significant signals in our data analysis. Thus, the lack of signal in the imbalance analysis does not necessarily mean that adverse events are not present, but may be due to insufficient reporting frequency or other factors that fail to show a signal. Finally, differences in healthcare quality may have an impact on how consistently drug safety is reported and assessed. Although data mining cannot replace professional assessment, it can have benefits when working with vast amounts of data that are examined to produce more thorough results. Examining AEs associated with edaravone revealed some unexpected potential AE signals that can direct future clinical investigations, despite the unavoidable limitations of the FAERS database employed in pharmacovigilance studies. To enhance the rigor of our research, we plan to adopt more advanced methods in the future, such as using electronic health records for propensity score matching to reduce confounding bias. Additionally, we will explore more detailed datasets to support case–control studies and closely monitor the accumulation of clinical trial data to conduct meta-analyses at the appropriate time. These improvements will not only strengthen the research design but also provide a more reliable evidence base for the safety assessment of Edaravone, thereby better guiding clinical practice and public health decision-making. Furthermore, Edaravone's effectiveness and safety need to be continuously observed.

## Conclusion

Using the disproportionality method, we performed a pharmacovigilance analysis based on actual data from the FAERS database to identify potential dangers and safety signals related to the usage of edaravone. The AEs found in this study were mostly in line with those listed, with several unexpected AEs, like abnormal hepatic function, catheter site thrombosis, pain, cerebral hemorrhage, infection, cerebral infarction, poor venous access, disseminated intravascular coagulation, vein collapse, and cerebral venous sinus thrombosis. The results of these signaling AEs somewhat augment the small number of clinical investigations conducted on this drug. To validate and clarify the causal relationship between edaravone and these AEs, more prospective clinical trials are necessary. This is because data analysis may be limited by confounding factors, demographic heterogeneity, inadequate data, and reporting bias. In addition, future researches can prioritize three methodological advancements to further address these limitations: (1) integration of electronic health records with propensity score matching to control confounding variables, (2) nested case–control studies utilizing standardized phenotyping protocols to establish temporal relationships, and (3) living systematic reviews incorporating global pharmacovigilance data streams. These tiered approaches will enable causal inference through sequential hypothesis testing while mitigating challenges related to demographic heterogeneity and surveillance bias. The findings of this study potentially provide valuable information for identifying hazards related to edaravone, supporting clinical monitoring and serving as a reference for future safety assessments of the drug.

## Data availability

This study was performed using the FAERS source that was provided by the FDA. The database used in this study is publicly available in website of https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files.

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## Author contributions

Qi Shang and Jie Zhou: Conceptualization, Methodology, Data curation, Formal analysis, Writing-review & editing. Maohua Chen and Junchang Ye: Data curation, Validation, Revision Funding acquisition, Supervision, Writing-review & editing. All authors approved the final version.

## Declarations

## Competing interests

The authors declare no competing interests.

## Ethics approval and consent to participate

Because this study was an observational study using global open database (FAERS) with anonymized information, not involving treatment intervention or collection of human samples, informed consent was exempted.

## Additional information

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