

## ORIGINAL RESEARCH

# Predicting the Risk of Opioid-induced Respiratory Depression Using ChatGPT-4o and Machine Learning Techniques

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**Abstract:** **Introduction:** Opioid-induced respiratory depression is a life-threatening complication of opioid overdose. This study aimed to develop a model for predicting the risk of respiratory depression following opioid overdose using ChatGPT-4o. **Methods:** A retrospective cross-sectional study was conducted on 2,005 patients admitted following opioid overdose at Loghman Hakim Hospital, Tehran, Iran, from February 2021 to February 2024. Demographic data, clinical presentations, interventions, and outcomes of patients were extracted from electronic medical records and a predictive model was developed using a no-code methodology with the assistance of ChatGPT-4o. **Results:** 2,005 patients with the mean age of  $32.97 \pm 14.86$  (Range: 1-100) years were studied (74.5% male). Respiratory depression was observed in 18% of patients upon admission. Naloxone was administered to 37.6% of patients, with higher usage in those requiring intubation. Key predictors included low oxygen saturation (SpO<sub>2</sub>), low respiratory rate (RR), and increased heart rate (HR). The predictive model achieved an accuracy of 94.4% (95% confidence interval (CI): 87.0-96.3), a recall of 81.0% (95% CI: 78.0-84.0) for respiratory depression, and an area under the curve (AUC) of 0.98 (95% CI: 0.95-0.99). **Conclusion:** The study highlights critical clinical predictors of respiratory depression risk in opioid overdose patients and demonstrates the potential of machine learning models in enhancing early detection and intervention.

**Keywords:** Opiate overdose; Respiratory insufficiency; Machine learning; Precision Medicine; Generative Artificial Intelligence

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## 1. Introduction

Respiratory depression is a critical and potentially fatal complication associated with opioid use and overdose (1). Defined by a reduction in both the rate and depth of breathing, it presents significant challenges in clinical settings, particularly in pain management and the treatment of opioid use disorders (2). Opioids, widely prescribed for their analgesic properties, function predominantly by activating  $\mu$ -opioid receptors within the central nervous system (3). While effective for pain relief, opioids can suppress the central respiratory

drive, leading to hypoventilation and subsequent hypoxemia (1, 3).

The severity of respiratory depression is influenced by various factors, including opioid dosage and potency, route of administration, and patient-specific characteristics such as age and existing cardiopulmonary conditions (4). Concurrent use of other central nervous system depressants like benzodiazepines further exacerbates the risk (5, 6). Clinically, opioid-induced respiratory depression manifests as diminished respiratory effort, with a respiratory rate falling below 6 breaths per minute and decreased oxygen saturation levels (SaO<sub>2</sub> < 94% and/or PaCO<sub>2</sub> > 6 kPa), potentially progressing to respiratory failure if not promptly addressed (7, 8).

Timely identification and intervention are essential to prevent severe outcomes, including hypoxia, hypercapnia, and cardiopulmonary arrest (1, 7). Management protocols in-

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involve supportive measures such as maintaining airway patency, administering supplemental oxygen, and utilizing mechanical ventilation when necessary (9). Opioid antagonists like naloxone are employed to competitively inhibit opioid receptors, effectively reversing respiratory depression (10). With the ongoing opioid epidemic impacting healthcare systems globally, the ability to accurately predict the occurrence of respiratory depression is increasingly vital for reducing its harmful effects (5). Early detection and prompt intervention can prevent life-threatening consequences, underscoring the importance of using technology in patient safety strategies (11).

Recent advancements in machine learning (ML) and artificial intelligence (AI) offer promising avenues for predicting adverse drug reactions, including opioid-induced respiratory depression (12, 13). By analyzing large datasets that encompass patient demographics, clinical variables, and pharmacological information, ML algorithms can identify complex patterns and risk factors not readily apparent through traditional statistical methods (14).

Techniques such as logistic regression, decision trees, random forests, and neural networks have been utilized to develop predictive models with high sensitivity and specificity (15). For instance, ML models can process real-time data from electronic health records (EHRs) to assess a patient's risk of respiratory depression during opioid therapy (16). Integrating these models into clinical practice can enhance monitoring and enable the development of personalized treatment plans (17). Moreover, AI-driven predictive analytics can aid in optimizing opioid dosing regimens by considering individual patient characteristics and potential drug interactions (18). This personalized approach can minimize the risk of respiratory depression while ensuring effective pain management (19).

This study aims to develop a predictive model for respiratory depression risk following opioid use by integrating basic demographic, clinical, and paraclinical data of patients with opioid poisoning and machine learning methodologies.

## 2. Methods

### 2.1. Study design and setting

This retrospective cross-sectional study was conducted on patients admitted following opioid overdose at Lohman Hakim Hospital (referral poisoning center), Tehran, Iran, from February 2021 to February 2024. Demographics, clinical presentations, interventions, and outcomes of patients were extracted from electronic medical records, which was thoroughly reviewed, and relevant data were systematically entered into a structured online form (Appendix-1). Finally, an outcome predictive model was developed using a no-code methodology with the assistance of ChatGPT-4o.

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval Code: IR.SBMU.RETECH.REC.1402.625). Patient confiden-

tiality was strictly maintained, and all data were anonymized before analysis. As this research utilized de-identified records obtained from the hospital's Health Information System (HIS), the requirement for individual informed consent was waived in accordance with institutional and national ethical guidelines. The study was conducted fully in compliance with the Declaration of Helsinki (2013 revision) and relevant national research ethics regulations.

### 2.2. Participants

The study included data from all patients hospitalized with opioid poisoning at the institution during the study period. None of the data was excluded from the study unless they were mistakenly recorded in the hospital registry system under the category "other narcotics," and a review of their records did not show any evidence of opium or opioid use. Additionally, due to the way the ages of individuals were recorded in the hospital system, the lowest registered age for patients was one year old, although it is possible that patients younger than this age may exist.

### 2.3. Data gathering

An online survey form was designed for data entry and preliminary analysis. Data collection continued until approximately 1,000 cases were entered, at which point the dataset was downloaded for initial analysis and to inform the training of predictive models. Data collection was subsequently extended until 2,000 cases were reached, after which the survey was closed and the complete dataset was downloaded for final analysis and model development.

Patients with opioid-induced respiratory depression were defined as those meeting any of the following criteria: exhibiting clinical signs of respiratory depression (respiratory rate <10 breaths per minute accompanied by hypoxia [ $\text{SpO}_2$  <94%]); or requiring endotracheal intubation either in the emergency department (ED) or during hospitalization.

Data were collected using a structured online form created in Persian, covering the variables listed in Appendix 1. The primary demographic variables included the patient's gender, age (in years), time of arrival at the ED, history of prior cardiopulmonary diseases, and substance use. Key objective measures from the patient's vitals and paraclinical data in the ED, such as clinical signs of respiratory depression, heart rate (HR), respiratory rate (RR), oxygen saturation ( $\text{SpO}_2$ ), evidence of respiratory acidosis in blood gas analysis (BGA), and data on interventions like naloxone administration, time to first naloxone dose (in minutes), and intubation, were also recorded. Additionally, data on patients' outcomes, such as the duration of hospital/intensive care unit (ICU) stay, duration of intubation, and status at discharge (discharge with/without sequelae, or deceased), were also collected and analyzed.

## 2.4. Data analysis and artificial intelligence application

### 2.4.1 Initial phase (to identify significant predictors)

The initial phase of the study involved analyzing a dataset that contained 1,015 patient cases using prompt engineering and a no-code methodology with the assistance of ChatGPT-4o. Table 1 demonstrates our prompts for this project. The purpose of this preliminary analysis was to identify significant predictors of opioid-induced respiratory depression and to build initial predictive models. These models aimed to uncover key factors contributing to respiratory depression in patients who had used opioids, which is a critical issue in clinical settings, especially in EDs and ICUs. The dataset included various variables, such as demographic information, medical history, vital signs, laboratory results, and clinical interventions. The goal was to use these variables to develop a model that could assist healthcare professionals in recognizing early signs of respiratory depression, which could potentially improve patient outcomes through timely interventions like naloxone administration.

Quantitative variables (e.g., age, heart rate, respiratory rate, oxygen saturation, duration of hospitalization, time to naloxone administration) were first assessed for normality using the Shapiro–Wilk test. Normally distributed variables were summarized as mean  $\pm$  standard deviation (SD), whereas non-normally distributed variables were presented as median (interquartile range). Between-group comparisons were conducted using independent-samples t-tests or Mann–Whitney U tests, as appropriate. Continuous variables were standardized (z-score normalization) before being entered into the predictive modeling pipeline to ensure equal weighting across features. For multivariate analyses, these variables were incorporated into logistic regression, random forest, and XGBoost classifiers to evaluate their independent association with respiratory depression.

Patients were grouped according to the presence or absence of opioid-induced respiratory depression, defined by pre-specified clinical criteria (respiratory rate  $<10$  breaths/min, SpO<sub>2</sub>  $<94\%$ , or need for intubation in ED). This dichotomous grouping (Respiratory Depression = Yes/No) served as the dependent outcome for all analyses and model training. Additionally, subgroup analyses were conducted based on opioid type (e.g., methadone, tramadol, opium) and clinical intervention status (naloxone use, intubation, ICU admission) to identify differences in outcomes and predictors. These groupings were chosen to align with established clinical definitions and to enhance the interpretability of the predictive model.

### 2.4.2 Second phase (to enhance the model's ability)

Once the preliminary analysis was complete and the first models were built, the dataset was expanded to include a total of 2,005 cases. This expansion aimed to enhance the model's ability to detect patterns in a larger, more diverse set of data, thus improving the generalizability of the model's predictions. The expanded dataset incorporated additional

patient demographics, clinical features, and paraclinical parameters, enabling a more comprehensive analysis of respiratory depression predictors. The expansion also served to address potential biases that might have existed in the initial dataset by introducing more variability within the data. With the expanded dataset in hand, the predictive models were retrained and validated to ensure that they performed optimally on the larger set. Retraining the models on the new dataset was essential to improving their accuracy and generalizability. It also allowed for fine-tuning of the algorithms to better handle more complex patterns in the data. The process of retraining and validation involved using prompt engineering for machine learning techniques such as logistic regression, decision trees, and random forests. These algorithms were selected because of their ability to handle both categorical and continuous variables, which were present in the dataset, and their suitability for building interpretable models that could provide insights into the key predictors of respiratory depression (20).

The predictive model was developed using prompt engineering on ChatGPT, including regularization methods (Ridge and Lasso Regression), Random Forests, Principal Component Analysis (PCA), followed by Logistic Regression, Cox Proportional Hazards Model, and Support Vector Machines (SVM). The dataset was split using an 80-20 training-validation ratio. The final model incorporated XGBoost, Voting Classifier, and Random Forest algorithms, achieving an accuracy of 94.4% (95% confidence interval (CI): 87-96.3).

Missing data were systematically reviewed prior to analysis. Variables with  $>10\%$  missing values were excluded from multivariate analyses to prevent bias. For continuous variables with 10% missingness, single imputation using the variable's median value was applied, while categorical variables were imputed using the mode. This approach minimized data loss while maintaining statistical integrity. All imputation procedures were performed using Scikit-Learn's preprocessing module within Python 3.11. A sensitivity analysis was conducted to confirm that imputation did not materially alter the results of the predictive models.

### 2.4.3 Third phase (to develop a web-based platform)

Once the predictive models were trained and validated on the larger dataset, the next step was to deploy them in a user-friendly platform for healthcare professionals. Given the growing need for real-time, accessible tools in clinical settings, the final predictive model was integrated into a web-based platform. This platform was developed using HTML, CSS, and JavaScript, three widely used technologies for creating interactive and dynamic web applications. The platform was designed with simplicity and usability in mind, ensuring that healthcare providers could easily navigate through it, input patient data, and interpret the results. The system allowed users to input key variables such as patient demographics, vital signs, and substance use history, and then provided immediate predictions regarding the likelihood of respiratory depression. In cases where the model predicted

a high risk, the platform could also recommend potential interventions, such as administering naloxone, performing cardiopulmonary resuscitation (CPR), or initiating other supportive measures. In addition to the web-based platform, an explainable artificial intelligence (XAI) model was incorporated into the system, making use of ChatGPT. Table 1 provides the prompt engineering pathway we used, and Appendix 2 contains links to our original prompts. What we requested from the custom GPT model was developed using the Generative AI (GAI) and Explainable AI (XAI) capabilities of ChatGPT-4o.

### 3. Results

#### 3.1. Data collection overview

Between February 20, 2021, and February 19, 2024, a total of 15,612 cases of opium and opioid admissions were recorded at Loghman Hakim Hospital in Tehran, Iran. Six authors concurrently entered this information into a structured online form to ensure efficient data collection. Upon reaching 1,015 cases, the initial dataset was downloaded for preliminary analysis and model training. Data collection continued until records for a total of 2,261 patients with opioid poisoning had been entered into the dataset.

Out of the 2,261 reviewed cases, 256 were excluded from the online form entry due to misclassification under the International Classification of Diseases, 10th revision (ICD-10) codes T40.4 (Other synthetic narcotics), T40.6 (Other and unspecified narcotics), or T40.9 (Other and unspecified psychodysleptics). Further evaluation of patient records revealed no evidence of opium or opioid use in these cases, indicating misclassification, which accounted for approximately 11.37% of the patients. Figure 1 demonstrates the flow of patients and the data collection process.

#### 3.2. Demographics and medical history

Among the final cohort of 2,005 patients, 1,494 (74.5%) were male and 511 (25.5%) were female, with a mean age of  $32.97 \pm 14.86$  (Range: 1-100) years and a median age of 30 (interquartile range (IQR): 21-41) years. The vast majority, 1,896 patients (94.5%), had no prior history of cardiopulmonary diseases, and 31.2% of patients were receiving methadone. The distribution of substances involved in overdoses was as follows: methadone in 625 (31.2%) cases, opium or opioids with other medications in 460 (22.9%) cases, tramadol in 368 (18.3%) cases, opium alone in 299 (14.9%) cases, mixture of opium/opioid with other medications and alcohol in 243 (12.1%) cases.

The median time to ED arrival was 9.0 (IQR: 6.0–13.0) hours. The most common arrival intervals were 2–4 hours (18.9%) and 4–6 hours (13.1%), while the time was not recorded in 16.8% of cases. Excluding cases with unknown arrival times, 42.6% arrived within 4 hours, 25.1% between 4–8 hours, 26.8% between 8–24 hours, 3.7% between 24–48 hours, and 0.8% after 48 hours. Compensated respiratory acidosis was

observed in 181 patients (9.0%), and uncompensated respiratory acidosis in 545 patients (27.2%). Naloxone was administered to 1180 (58.8%) patients either in the ED or pre-hospital setting. 243 (12.11%) patients required intubation and 161 (8.0%) patients were admitted to the ICU (Of these, five patients were re-admitted to the ICU after initially being transferred to the ward, primarily due to respiratory depression and uncompensated respiratory acidosis).

1712 (85.4%) cases were discharged without sequelae, 221 (11.0%) cases left the hospital against medical advice, 7 (0.3%) cases were discharged with sequelae, and 65 (3.2%) cases expired. Table 2 compares the demographic characteristics of patients with and without respiratory depression during their ED visit or hospitalization.

#### 3.3. Feature importance analysis

The feature importance analysis identified the top features contributing to the model's predictions:

All variables included in our statistical analysis showed significant differences between patients with and without respiratory depression. In the model's feature analysis, oxygen saturation in the emergency department ( $SpO_2$ ) emerged as the strongest predictor of respiratory depression ( $p < 0.001$ ). Respiratory rate in the ED ( $p < 0.001$ ) and heart rate in the ED ( $p < 0.05$ ) were also important vital-sign predictors reflecting respiratory status. Additionally, time to first naloxone administration ( $p < 0.001$ ) and duration of hospitalization ( $p < 0.001$ ) served as indicators of treatment timeliness and clinical severity. Table 3 demonstrates the primary data analysis of 1015 patients and ChatGPT's prediction for 2000 patients in comparison to the actual data analysis of 2005 patients. Figure 2 demonstrates the correlation matrix of all features in the final 2005 patients after normalization. The final Explainable AI (XAI) model, which is available as a chatbot in <https://chatgpt.com/g/g-ZQUsxUwI7-loghman-opioid-respiratory-depression-predict-gpt>, emphasizes the importance of vital signs and timely interventions. However, it did not directly correlate respiratory rate and heart rate with clinical manifestations of respiratory depression through statistical analysis. The prompts and chats are included in Appendix 2.

#### 3.4. Model performance

The model demonstrated the accuracy of 94.4% (95% CI: 87–96.3) in predicting the absence of respiratory depression, which can aid in reducing unnecessary naloxone administration or intubation, allowing healthcare professionals to focus on high-risk patients. However, the model's recall for respiratory depression was moderate, correctly identifying 81% (95% CI: 78–84) of at-risk patients while missing 19%. The Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) were excellent at 0.98 (95% CI: 0.95–0.99), indicating strong discriminative ability between patients with and without respiratory depression.

Confusion matrix results were as follows: true negatives 321,

false positives 5, false negatives 17, and true positives 73. The confusion matrix revealed that respiratory depression (Class 1) was less prevalent compared to patients without experiencing respiratory depression (Class 0), which is typical in clinical datasets with imbalanced outcomes. The model exhibited high precision (95%) and recall (98%) for Class 0 and moderate performance for Class 1 with an 81% (95% CI: 78-84) recall, indicating room for improvement in identifying all at-risk patients.

#### 4. Discussion

Opioid-induced respiratory depression remains a significant clinical challenge due to its potential for fatal outcomes (1). In our study, 18% of the 2,005 patients presented with clinical signs of respiratory depression upon admission, highlighting the critical nature of this complication. This prevalence aligns with existing literature, which reports respiratory depression in 15–30% of opioid overdose cases (21). Methadone and other potent opioids were frequently associated with severe respiratory compromise, consistent with previous findings that link higher opioid potency and longer half-life to increased risk (1, 7, 22).

Among the total 2005 cases, 7.8% of patients required intubation, and 8.03% were admitted to the ICU. Patients exhibiting respiratory depression were more likely to require intubation (17.5%). These findings corroborate prior studies emphasizing the need for advanced respiratory support in severe overdose cases (23). The mortality rate in our study was 3.2%, which is comparable to other studies reporting mortality rates between 2% and 5% among hospitalized opioid overdose patients receiving timely interventions (24-26). This indicates the effectiveness of prompt medical management, including naloxone administration and ventilatory support.

Key clinical parameters such as low oxygen saturation (SpO<sub>2</sub>), decreased respiratory rate (RR), and increased heart rate (HR) proved to be significant predictors of respiratory depression. These vital signs are critical for the acute management of overdose patients, as supported by other research (6, 23, 27). Early identification of patients at risk allows for timely interventions that can prevent progression to respiratory failure.

Time to first naloxone administration emerged as another predictive variable for respiratory depression in patients with opioid poisoning. As shown in Table 2, the time to initial naloxone administration was significantly longer in patients who developed respiratory depression compared with those who did not (420 min vs. 180 min). This finding aligns with previous observations indicating that timely naloxone administration reduces the likelihood of respiratory depression and mortality in opioid overdose (28). Continuous monitoring remains essential to identify late-onset respiratory depression, which may occur due to re-exposure, delayed opioid absorption, or drug redistribution (29).

A novel aspect of this study was the utilization of ChatGPT-4® for data analysis and predictive modeling. Logistic regres-

sion was used as the foundational algorithm due to its simplicity and effectiveness in binary classification tasks, such as predicting whether a patient is at risk for respiratory depression or not. This method provided a probabilistic output that could quantify the likelihood of an event occurring based on various predictor variables. It allowed for an initial understanding of how specific factors (e.g., age, opioid type, vital signs) contributed to the likelihood of respiratory depression (30). Decision trees, on the other hand, were employed to visualize the decision-making process behind the predictions. These trees offered an intuitive way to understand the relationships between different variables and how they influenced the risk of respiratory depression. Decision trees helped identify thresholds at which certain variables, such as heart rate or oxygen saturation, could lead to a higher risk of respiratory depression, making it easier for clinicians to interpret the results in real-time (31, 32). Random forests, an ensemble learning method, were also used to improve the accuracy and robustness of the models. By aggregating multiple decision trees, random forests helped mitigate overfitting, an issue that could arise when a model is too closely tied to the specifics of the training data. Random forests also provided better performance by capturing more complex interactions between the predictors and by reducing variance compared to individual decision trees. This made them particularly valuable for improving the overall predictive power of the model (33, 34). The artificial intelligence (AI) system achieved a high accuracy of 94.4% (95% CI: 87-96.3) in predicting the absence of respiratory depression, offering a potential tool to help clinicians prioritize at-risk patients and optimize resource allocation. While the model's recall for respiratory depression was 81% (95% CI: 78-84), indicating some missed cases. However, the overall performance is promising (12). The high area under the receiver operating characteristic curve (AUC) of 0.98 (95% CI: 0.95-0.99) demonstrates strong discriminative ability (35). The use of ChatGPT allowed for a more interactive and explanatory approach to the predictions. Healthcare professionals could engage with the AI model through a chatbot interface, asking questions about the model's predictions and receiving detailed, understandable explanations in real time. This conversational AI feature was particularly valuable for clinicians who may not be familiar with the underlying machine learning algorithms but needed to understand the rationale behind a prediction. The integration of the AI chatbot also helped address concerns about the "black-box" nature of many machine learning models. By providing understandable explanations of the predictions, the system promoted better collaboration between human clinicians and AI, fostering a more confident and informed decision-making process. This was particularly important in critical care settings, where timely interventions can mean the difference between life and death (36-38). Integrating AI models like ChatGPT-4® into clinical workflows could enhance early detection of adverse outcomes, particularly in resource-limited settings (19).

However, the moderate recall rate suggests that the model may benefit from further improvements. Incorporating additional clinical variables or employing more advanced algorithms, such as deep learning techniques, might refine predictive performance (39). Moreover, external validation with larger and more diverse populations is necessary to enhance validity (40).

While we aimed to design an AI model to effectively predict respiratory depression, its ability to forecast other critical outcomes, such as long-term neurological sequelae or the need for re-admission to the ICU, remains unclear. Future research should aim to develop multi-outcome predictive models to provide a more comprehensive risk assessment (41).

#### 4.1. Potential biases in this study

We acknowledge that, as a retrospective single-center study, our analysis is inherently subject to several potential sources of bias. The main sources and their likely directions are as follows:

1. Selection bias: The study population was drawn exclusively from patients admitted to a tertiary referral hospital. This may over-represent more severe opioid-poisoning cases and inflate the apparent prevalence and severity of respiratory depression compared to the general opioid-using population. Consequently, the magnitude of predictive accuracy observed in our model may be slightly overestimated when applied to broader clinical settings.

2. Information bias (misclassification): Diagnostic coding errors in the hospital's Health Information System (HIS) led to the exclusion of approximately 11.37% of initially retrieved records due to incorrect ICD-10 classification. Although this correction improved data validity, any residual misclassification could bias the estimated associations toward the null, leading to a conservative estimate of variable significance. 3. Measurement bias: Vital signs and laboratory measurements were recorded by different clinicians under emergency conditions, introducing minor inter-observer variability. This variability is likely non-differential and therefore would attenuate, rather than exaggerate, associations between predictors and outcomes.

4. Missing data bias: Missingness was mostly random and limited (<10% for key quantitative variables). Median/mode imputation was used, which may slightly reduce variance in continuous variables and thus underestimate the strength of associations in multivariate models. 5. Model bias: The use of machine-learning models trained on retrospective data may lead to overfitting, particularly given the moderate class imbalance (18% of cases with respiratory depression). We mitigated this by employing cross-validation, regularization (Ridge/Lasso), and feature scaling, but residual optimism in performance metrics cannot be excluded.

6. Generative AI Hallucination: Recognizing the potential for hallucinated or inaccurate outputs common to AI assistants, we thoroughly validated its results through our statistician

(H.J.) and conventional machine learning techniques run by I.A. Both evaluations revealed no significant discrepancies, likely thanks to effective prompt engineering. Throughout, we used prompts designed to replicate the expertise of a professional statistician or computer scientist, including the use of Python LABs when necessary.

Overall, the net direction of bias in this study is toward conservative estimates; that is, any real associations between clinical predictors and respiratory depression may be stronger than observed. The magnitude of potential bias is considered modest given the large sample size ( $n = 2005$ ), low rate of missingness, and corrective measures implemented during data cleaning and model validation.

## 5. Limitations

Potential limitations of this study include the retrospective design that may introduce selection and information biases due to reliance on existing medical records (42), lack of validation cohort and recruiting patients from only one hospital are other limitations of this study (43), also the identification of approximately 11.37% misclassified cases underlines the importance of accurate data entry in electronic health records and the reliance on accurate record-keeping within the HIS database (44). Additionally, while machine learning models offer powerful predictive capabilities, their performance is dependent on the quality and completeness of the input data (45); the relatively small number of patients experiencing respiratory depression limits the statistical power for certain analyses and may affect the robustness of the predictive model (46); also the necessity of using paid versions and the time limitations in the paid versions, in terms of access to model editing as well as the continuation of statistical analyses, can be considered as technical limitations we confronted in this project.

## 6. Conclusions

Our findings demonstrate that machine-learning models, developed with the support of generative artificial intelligence, can reliably predict respiratory depression using readily available clinical variables. Such tools have the potential to strengthen clinical decision-making, streamline triage processes, and probably improve patient outcomes. Integrating these predictive approaches into routine care, alongside continued efforts to enhance data quality and system-wide digital infrastructure, may enable healthcare systems to better respond to the growing burden of opioid-related admissions and reduce preventable morbidity and mortality.

## 7. Declarations

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University of Medical Sciences, Tehran, Iran, for their support, cooperation, and assistance throughout the period of study.

### 7.2. Authors' contributions

Sh.Sh., and M.M. developed the initial concept and proposal for the study. The data collection team (A.F., F.E., M.A., P.E., N.B., and S.K.) meticulously reviewed electronic patient files and extracted necessary information into a structured web-based form. Any uncertainties or issues encountered during data entry were escalated to Sh.Sh., P.E.T.E., and M.M. for resolution.

After data entry, the information was translated into English to facilitate interpretation by machine learning models. M.M. and F.Z. were responsible for data analysis and model development using ChatGPT, while I.A. and N.R.R. focused on model training using standardized AI training protocols. The introduction was collaboratively authored by H.J., Sh.A.E., K.Kh., S.M.H., and M.A., whereas the methods and results sections were written by M.M., I.A., H.J., S.M.H., and N.R.R. The discussion was collaboratively authored by S.M.H., B.M., M.R., and P.E.T.E., and the final report was developed through the joint efforts of all authors.

### 7.3. Ethics approval

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.RETECH.REC.1402.625.

### 7.4. Funding statement

None.

### 7.5. Data availability statement

Data will be made available on request.

### 7.6. Declaration of competing interest

The authors declare that they have no conflict of interest.

### 7.7. Using artificial intelligence chatbots

Used artificial intelligence chatbots in analyzing, creating images, and language editing.

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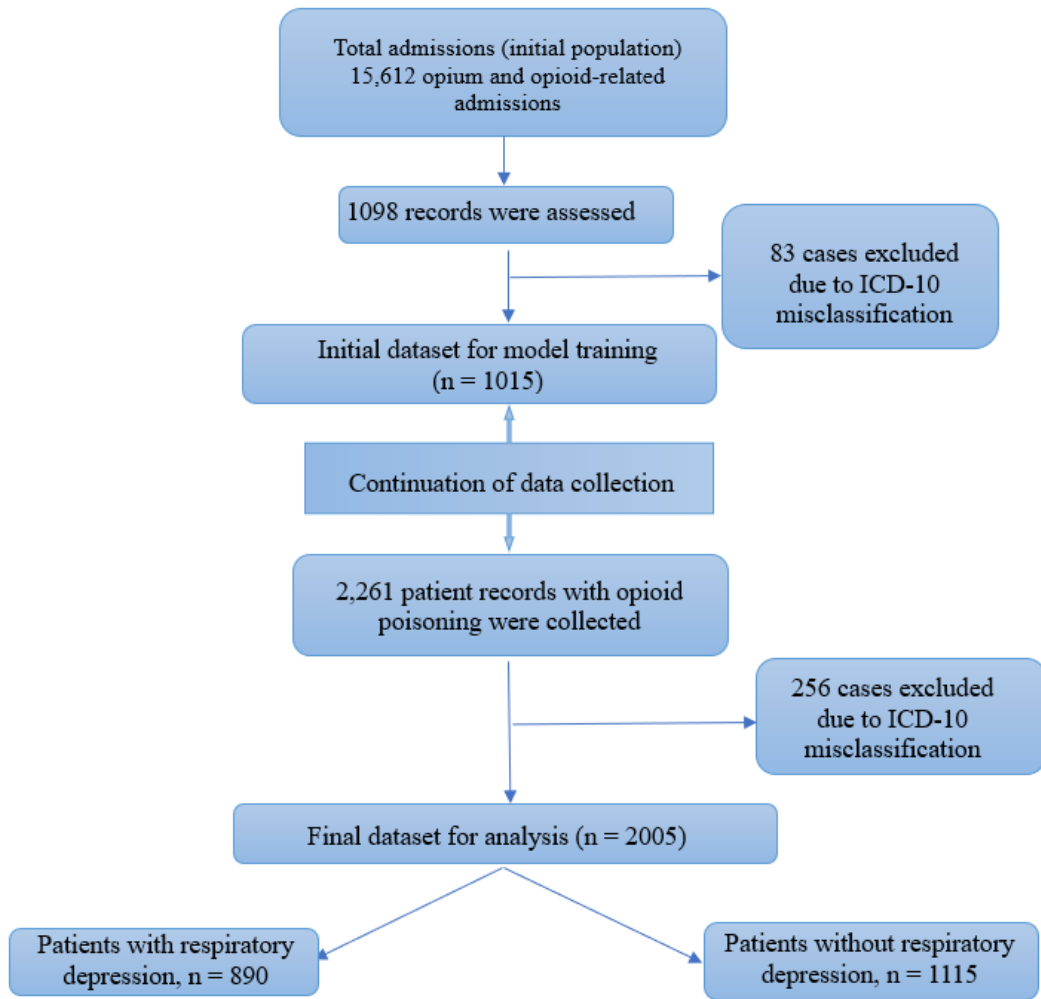


Figure 1: Flowchart for the flow of patients.

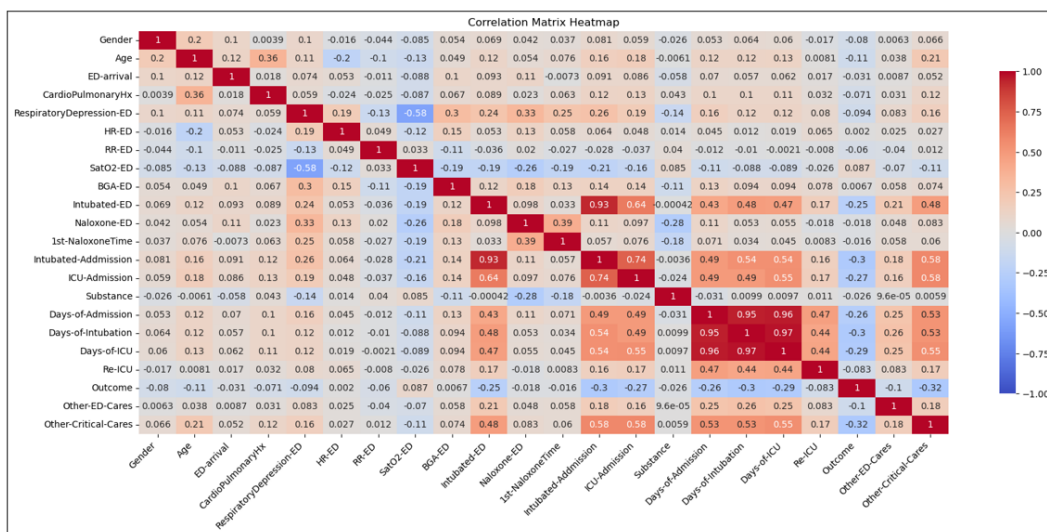


Figure 2: Correlation Matrix for All features (After Normalization and Standardization). ED: emergency Department; HR: Heart Rate; RR: Respiratory Rate; SatO2: Peripheral Oxygen Saturation; BGA: blood gas analysis; ICU: Intensive Care Unit.

**Table 1:** Prompts used during the study

First, we asked Chat-GPT-4o@ to provide a prompt in the role of a medical epidemiologist for data analysis:	As a role of medical epidemiologist, give me a prompt for 1- gathering data 2- cleaning and sorting data 3- analyzing each variable for their quantitative or qualitative distribution by p-values assessment 4- assess relevancy of variables all together 5- summarize these data in a table and visualize them by charts 6- filter and remove cases with specific variable (ask me for what to do) 7- analyze above mentioned (steps 2, 3, and 4) for the new data 8- summarize data of unfiltered and filtered data together in a table for comparison 9- visualize data by charts for comparison 10- write and report these steps for methods and results section of a medical academic paper
As it generated the specific prompt, we modified each section and proceeded with them as follows:	
1- Data Gathering: After uploading the spreadsheet to Chat-GPT-4o@, we used this prompt for specific data gathering:	As a medical epidemiologist, gather data from this spreadsheet. Ensure to include variables such as patient demographics (age, gender, cardiopulmonary disease history, substance use), clinical characteristics (clinical parameters in emergency department, comorbidities, respiratory depression, blood gases analysis for neither or compensated or uncompensated respiratory acidosis), treatments (naloxone administration, intubation, ICU admission), and final outcomes. Collect data for a sufficiently large sample size to ensure statistical validity.
2- Cleaning and Sorting Data:	Clean and sort the gathered data by removing duplicate entries, correcting errors, and standardizing formats. Handle missing values appropriately by either imputing them or excluding them based on the extent and nature of missingness. Ensure that categorical variables are coded consistently, and numerical variables are within plausible ranges.
3- Analyzing Data-Set in Both Quantitative and Qualitative Variables:	Analyze each variable individually to understand its distribution. For quantitative variables, calculate measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range). For qualitative variables, calculate frequencies and proportions. Use appropriate statistical tests (e.g., t-tests, chi-square tests) to assess the significance of each variable's distribution and calculate p-values to determine the likelihood of observing the data under the null hypothesis 4- Relevancy Analysis: Assess the relevancy of all variables together by performing multivariate analyses such as logistic regression or Cox proportional hazards models. Identify which variables are significantly associated with the respiratory depression signs, i.e. clinical manifestation, naloxone administration, or intubation, while controlling for potential confounders. Evaluate the overall model fit and the contribution of each variable to the model and to the final outcome of the patients.
5- Data Visualization and Comprehensive Table:	Summarize the data in a comprehensive table that includes descriptive statistics for each variable and the results of the univariate and multivariate analyses. Create visualizations such as histograms, bar charts, box plots, and scatter plots to illustrate the distribution of variables and the relationships between them. Ensure the charts are clear and informative, with appropriate labels and legends.
6- Excluding Unknown ED Arrivals and Comparative Data Analysis:	Identify cases with an "unknown" time of ed-admission, they needed to be filtered or removed. Please specify the variable and the criteria after filtering and removing. Then repeat steps 2, 3, and 4 for the filtered data set. Clean and sort the new data, analyze each variable for its distribution and significance, and assess the relevancy of all variables together in the context of the new dataset. Finally Compare the findings to those obtained from the original unfiltered data.
7,8- Visualization and Table Formation:	Create a comparative table that summarizes the key statistics and results from both the unfiltered and filtered data sets. Highlight any significant differences or changes in the distribution and relevance of variables between the two datasets. Generate visualizations to compare the unfiltered and filtered data. Use side-by-side bar charts, box plots, and other comparative charts to illustrate how the filtering process affected the data. Ensure the visualizations clearly show the differences and similarities between the datasets.
9- Reporting Findings in the Format of a Medical Paper's Author:	Document the methods and results of your analysis in a structured format suitable for a medical academic paper. In the Methods section, describe the data sources, the data cleaning and sorting procedures, the statistical analyses performed, and the criteria for filtering cases. In the Results section, present the key findings, including tables and charts summarizing the data distributions, significance tests, and multivariate analyses for both the unfiltered and filtered datasets. Discuss the implications of the findings and any limitations of the study.
10- Prediction for a Dataset of 2,000 Cases:	What would be your prediction if there were 2000 opioid overdose cases?
11- Analysis of 2,005 Cases: Subsequently, we started a new chat by uploading our data-set of 2,005 cases, labeled as "Opioid-Cases-2000-EN," and followed the aforementioned prompts for this data-set as well. For the final assessment, we asked this chat to compare its results with the prediction from the previous chat for 2,000 cases. (Results are demonstrated in Table 3.)	
### Predictive Analysis for 2000 Opioid Overdose Cases Based on the findings from the analysis of 1000 opioid overdose cases, we can make some predictions for a dataset with 2000 cases. Here are the steps and the expected outcomes: ##### Methodology 1. **Scaling the Current Findings:** - Assuming the distribution and characteristics of the additional 1000 cases are similar to the initial 1000 cases. - Predicting values for demographic, clinical, and outcome variables based on the observed means, medians, and proportions. 2. **Expected Distributions: ** - **Demographics:** - **Gender:** The gender distribution (approximately 75% male and 25% female) is likely to remain consistent. - **Age:** Mean age around 32 years with a similar standard deviation. 3. **Clinical Characteristics and Outcomes:** - **HR-ED, RR-ED, Sat-ED:** Expected to maintain their means and standard deviations. - **Intubated-ED and ICU-Admission: ** Proportions are expected to remain stable. - **Respiratory Depression-ED:** Likely to remain around the same proportion observed. ##### Predictions 1. **Demographic Distribution:** - **Gender:** Approximately 1500 males and 500 females. - **Age: ** Mean age around 32 years with similar variability. 2. **Clinical Characteristics:** - **HR-ED:** Mean around 88 bpm. - **RR-ED: ** Mean around 17 breaths per minute. - **Sat-ED: ** Mean around 94%. - **Days_of_Admission:** Mean around 2.39 days, with variability similar to the current dataset. 3. **Outcomes: ** - **Respiratory Depression -ED: ** Expected to occur in about 21% of cases (assuming similar distribution). - **Intubated-ED:** Approximately 6% of cases. - **ICU-Admission: ** Approximately 6% of cases. - **Well Discharged:** Around 79% of cases. ##### Summary Table for Predictions   Variable   Prediction for 2000 Cases   -----  -----   **Gender**   1500 males, 500 females    **Age**   Mean 32 years    **HR-ED**   Mean 88 bpm    **RR-ED**	

**Table 1:** Prompts used during the study

<p>  Mean 17 breaths/min   <b>Sat-ED</b>   Mean 94%   <b>Days_of_Admission</b>   Mean 2.39 days   <b>Respiratory Depression-ED</b>   420 cases (21%)   <b>Intubated-ED</b>   120 cases (6%)   <b>ICU-Admission</b>   120 cases (6%)   <b>Well Discharged</b>   1580 cases (79%)   ### Discussion These predictions assume that the additional 1000 cases are similar in characteristics to the initial 1000 cases analyzed. This includes demographic distributions, clinical parameters, and outcomes. The predictions should be validated with the actual data once available to ensure accuracy and identify any deviations or new patterns. ### Limitations - <b>Assumption of Similarity:</b> The predictions are based on the assumption that the new cases will have similar characteristics to the current dataset. Any significant deviation in the new dataset can affect the accuracy of these predictions. - <b>External Factors:</b> Changes in external factors such as healthcare practices, the availability of naloxone, or changes in the population can influence the characteristics of the new cases. Here's a prediction for about 2000 opioid overdose cases, how similar are these predictions to your analysis? Report in statistics and p-value analysis.</p>
<p>12- Detailed Similarity Assessment: I mean how similar are these 2000 datasets to your analysis of about 2000 patients</p>
<p>13- Prediction Model Creation: That's great Now I need you to make a prediction model. First, we will input the demographic values like age, gender, cardiopulmonary history, and clinical manifestations of HR, RR, SatO2 in ED, type of substance, and time to ED arrival. Then you will process the data and give the results whether the patient is in respiratory depression or not, may benefit from naloxone administration or intubation? And how would be his or her final outcome, and days of admission?</p>

**Table 2:** Demographic characteristics of patients with and without opioid-induced respiratory depression

Variables	Total (n = 2005)	Respiratory Depression		P value
		Yes (n = 890)	No (n = 1115)	
Age (year), mean (SD)	32.97 (14.86)	35.07 (17.20)	31.29 (15.27)	0.007
Male/Female ratio, n (%)	1494:511 (2.92:1)	693:197 (3.51:1)	801:314 (2.55:1)	0.463
ED arrival time (hours), median (IQR)	9 (6-13)	10 (7-18)	9 (4-12)	0.589
History of cardiopulmonary diseases, n (%)	109 (5.4)	63 (7.1)	46 (4.1)	0.339
Methadone, n (%)	625 (31.2)	634 (71.3)	358 (32.1)	0.082
HR (/min), mean (SD)	94.29 (27.4)	108.70 (33.2)	79.88 (21.7)	<0.05
RR (/min), mean (SD)	16.89 (3.5)	9.73 (2.5)	16.02 (3.8)	<0.001
SpO <sub>2</sub> (%), mean (SD)	93.35 (4.4)	90.16 (3.6)	95.90 (4.2)	<0.001
Uncompensated blood gas analysis, n (%)	545 (27.18)	341 (38.3)	204 (18.3)	<0.01
Naloxone administration, n (%)	1180 (58.8)	753 (84.6)	427 (38.3)	<0.01
First naloxone administration time (min), median (IQR)	240 (120-550)	420 (300-600)	180 (120-240)	<0.001
Intubated Patients, n (%)	243 (12.11)	156 (17.5)	87 (7.8)	<0.001
Duration of Intubation (day), median (IQR)	1.65 (1-3)	2.3 (1.3-5)	1 (0.5-2)	<0.001
ICU stay (day), median (IQR)	2.3 (1-4)	3.41 (2-6)	1.2 (1-4)	<0.001
Duration of Hospitalization (day), median (IQR)	3.65 (1-5)	4.7 (3-8)	2.6 (1 -5)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or frequency (%).  
SD: Standard Deviation; IQR: Interquartile Range; ED: emergency Department; ICU: Intensive Care Unit; HR: Heart Rate; RR: Respiratory Rate; SpO<sub>2</sub>: Peripheral Oxygen Saturation; min: Minute; n: Number.

**Table 3:** Comparison of analyses between initial 1,015 patients, predicted 2,000 patients, and actual 2,005 patients

Variable	Analysis of 1015 cases	Prediction for 2000 cases	Actual 2005 cases
Gender (Male), n (%)	748 (73.7)	~1500 (75)	1494 (74.5)
Age (years), mean (SD)	32.07 ± 14.36	Mean ~32	32.97 ± 14.86
Cardiopulmonary (No), n (%)	949 (93.5)	~1898 (94.9)	1896 (94.6)
Substance (Methadone), n (%)	314 (30.9)	~628 (31.4)	625 (31.2)
Respiratory Depression (No), n (%)	788 (77.63)	~1093 (54.65)	1115 (55.6)
HR (bpm), mean (SD)	88.15 ± 18.77	Mean ~94	94.29 ± 27.4
RR (breaths/min), mean (SD)	16.98 ± 3.89	Mean ~17	16.89 ± 3.5
SatO <sub>2</sub> (%), mean (SD)	93.79 ± 6.22	Mean ~94	93.35 ± 4.4
Acidosis in BGA (No), n (%)	600 (59.11)	~1200 (60)	1279 (63.8)
Intubation (No), n (%)	949 (93.5)	~1798 (89.9)	1762 (87.8)
ICU Admission (No), n (%)	949 (93.5)	~1823 (91.15)	1844 (92)
Discharged (Yes), n (%)	787 (77.5)	~1580 (79)	1712 (85.4)
Duration of Hospitalization (days), median (IQR)	3.58 ± 1.65	Median ~3.58	3.65 (1-5)

Data are presented as %. CI: confidence interval.

**Appendix 1:** English translation of structured online form for data entry

<b>Primary Demography</b>	
Patient ID	Raw data entry
Gender	Male   Female
Age (in years)	Raw data entry Rounded to the nearest whole number (e.g., a patient aged 3 months was recorded as 1 year old; a patient aged 46 years and 8 months was recorded as 47 years old)
Time to ED-arrival	Multiple choice question Less than 10 minutes 10 – 30 minutes 30 minutes to 1 hour 1-2 hours 2-4 hours 4-6 hours 6-8 hours 8-12 hours 12-24 hours 24-48 hours more than 48 hours
Cardiopulmonary diseases previous history	Yes   No
The substance type for patient overdose	Multiple choice question Opium Opioids except Methadone and Tramadol Mixture of Opium and Opioids Mixture of Opium and Opioids with other medications Mixture of Opium and Opioids with alcohol Mixture of Opium and Opioids with alcohol and other medications Tramadol Methadone
<b>Findings in the ED</b>	
Manifestations of respiratory depression (RR<10/min, SatO2<90%, Apnea)	Yes   No
Heart Rate (per minute)	Raw data entry
Respiratory Rate (per minute)	Raw data entry
SatO2 (per cent)	Raw data entry
Blood Gas Analysis of Respiratory Acidosis (for standardized approach in interpretation we used this online calculator: <a href="https://www.mdcalc.com/calc/1741/arterial-blood-gas-abg-analyzer">https://www.mdcalc.com/calc/1741/arterial-blood-gas-abg-analyzer</a> )	Multiple choice question No Yes - Compensated Yes - Uncompensated
<b>ED or EMS demography</b>	
Intubate in ED or before reaching hospital	Yes   No
Naloxone administration in ED or before reaching hospital	Yes   No
The first dose of naloxone administration after overdose (in minutes)	Raw data entry (0 if no naloxone administered)
Does the patient get CardioPulmonary Resuscitation (CPR), Dialysis, or Central Venous (CV) Catheter in the ED?	Yes   No
<b>Disposition</b>	
Was patient intubated during admission?	Yes   No
Was patient admitted to the Intensive Care Unit (ICU)?	Yes   No
Days of admission	Raw data entry
Days of intubation	Raw data entry (0 if not intubated)
Days of ICU-admission	Raw data entry (0 if not admitted to the ICU)
Was the patient re-admitted to the ICU after transferring to the ward (if applicable)	Yes   No
Does the patient get Cardiopulmonary Resuscitation (CPR), Dialysis, or Central Venous (CV) Catheter during admission?	Yes   No
Final Outcome	Multiple choice question Well Discharged Partial Recovery Discharged with Morbidity or Any Sequelae Expired Left hospital against medical advice (Lost to Follow-Up)

ED: emergency department; RR: respiratory rate; SatO2: O2 saturation; EMS: emergency medical services.

**Appendix 2:** The Prompts are achievable through these links for further studies

- First prompt for data-analysis:  
<https://chatgpt.com/share/60c5ef44-9bac-4200-86e3-c938fc801187>
- Prompts for analysis of 1000 cases:  
<https://chatgpt.com/share/bf071720-2e87-4765-93c7-344ae16418d7>
- Prompts for analysis of 2000 cases, prediction model formation and customGPT-making:  
<https://chatgpt.com/share/424054a4-b0de-449d-9c53-55802305c4ae>
- Prompts for analysis of subgroups, prediction model formation in html-javascript and customGPT:  
<https://chatgpt.com/share/671167f0-e568-8006-9bf5-8d8dcaa35cae>
- Google-CoLAB link for using processing power and prediction model formation:  
<https://colab.research.google.com/drive/1ynnQKYTR01cOK12OCqFuVVvAxbHeDt1?usp=sharing>
- Chatbot Generated Preeducated Transfer (GPT) for prediction model:  
<https://chatgpt.com/g/g-ZQUsxUwI7-loghman-opiorespdeppredict-gpt>

.....  
Recommended prompt model:

According to the following data, please predict the patient's condition and probability of overdose, need for naloxone, intubation, ICU admission, length of stay, and final outcome?

Age: (e.g., 65)

Gender: (e.g., Female/Male)

Substance Exposure Type: (e.g., Opium smoke, Heroin injection)

Time Since Exposure: (in hours, e.g., 4 hours)

Heart Rate (HR): (in bpm, e.g., 67)

Respiratory Rate (RR): (in breaths per minute, e.g., 10)

Oxygen Saturation (SatO2): (as a percentage, e.g., 89%)

Cardiopulmonary History: (Yes/No; if Yes, specify conditions, e.g., Hypertension, COPD)

Other Symptoms: (e.g., Drowsiness, Confusion, Seizures, No other symptoms)

Current Medications: (e.g., Amlodipine, Beta-blockers)

- .....
- A chat with CustomGPT (loghman-opiorespdeppredict-gpt) in Persian language:

<https://chatgpt.com/share/671168ec-36ac-8006-90ce-8d3cb4f48b50>

- Two chats CustomGPT (loghman-opiorespdeppredict-gpt) in English language:

<https://chatgpt.com/share/67116c57-596c-8006-8b9d-9857d7984ca8>

<https://chatgpt.com/share/67116c6b-a470-8006-8126-695ac69b652c>

- How to integrate API with customGPT (loghman-opiorespdeppredict-gpt):

<https://chatgpt.com/share/6711ac0f-9494-8006-8c15-001142ada96d>