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POLYPHARMACY PARADOX: UNRAVELING ENTERIC ULCER CONUNDRUM

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ABSTRACT: Background/Aims: Polypharmacy, the concurrent use of multiple medications by a single patient, is common in modern healthcare to manage multiple comorbidities. While it helps address complex health conditions, it also brings significant challenges, such as increased risks of drug interactions and adverse effects, including the development of enteric ulcerlesions in the gastrointestinal tract. **Methods:** This research paper examines the complex relationship between polypharmacy and enteric ulcer formation through a comprehensive literature review. It investigates the mechanisms behind enteric ulcer development and the impact of polypharmacy on gastrointestinal physiology. **Results:** By analyzing the interactions and consequences of multiple medications on gastrointestinal health, this paper provides valuable insights for clinicians. These insights are aimed at optimizing medication regimens to reduce the risk of enteric ulcers and enhance patient outcomes. This paper aims to clarify the paradox of polypharmacy in relation to enteric ulcer formation. It highlights the complex interactions between multiple medications and gastrointestinal health, offering guidance for healthcare professionals. This guidance is essential for balancing the therapeutic benefits of polypharmacy against its potential risks, particularly the development of enteric ulcers. **Conclusions:** Through this detailed review, the paper contributes to a better understanding of effective polypharmacy management, ensuring patients receive the most beneficial and least harmful medication combinations.

INTRODUCTION: Polypharmacy, a term originating from the Greek roots "poly" meaning many and "pharmacy" referring to the medications, denotes the concurrent use of multiple medications by an individual[1]. While polypharmacy has become increasingly prevalent in modern healthcare, its significance lies in both its therapeutic potential and the complexities it introduces to patient care [2].

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In the pursuit of managing chronic conditions, comorbidities and age-related ailments, healthcare providers often prescribe multiple medications to address diverse aspects of a patient's health [3]. However, this practice raises concerns regarding drug interactions, adverse effects, medication adherence, and overall patient safety [4].

Impact of Polypharmacy on Gastrointestinal Physiology: Polypharmacy, characterized by the concurrent use of multiple medications, exerts a multifaceted impact on gastrointestinal (GI) physiology, encompassing alterations in gastric acid secretion, disruption of mucosal integrity, modulation of gastrointestinal motility and blood

flow, and perturbation of the gut microbiota [5, 6]. Understanding these effects is crucial for mitigating the risk of gastrointestinal complications, including enteric ulceration, associated with polypharmacy regimens [7, 8].

Effects of Medications on Gastric acid Secretion: Various medications commonly prescribed in polypharmacy regimens can modulate gastric acid secretion, thereby influencing the gastric luminal environment and mucosal integrity. Proton pump inhibitors (PPIs), histamine H2-receptor antagonists, and antacids are commonly employed to reduce gastric acid secretion, providing relief for conditions such as gastroesophageal reflux disease (GERD) and peptic ulcer disease [9, 10]. In contrast, medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and selective serotonin reuptake inhibitors (SSRIs) can increase gastric acid production, which may predispose individuals to gastrointestinal complications related to acid secretion [11, 12].

Disruption of Mucosal Integrity by Certain Drugs: Polypharmacy can lead to the disruption of mucosal integrity through direct cytotoxic effects, impairment of mucous and bicarbonate secretion, and inhibition of mucosal repair mechanisms. NSAIDs, particularly cyclooxygenase-1 (COX-1) inhibitors, exert their ulcerogenic effects by inhibiting prostaglandin synthesis, reducing blood flow to the mucosal lining and weakening the protective barrier of the gastric mucosa [13]. Similarly, corticosteroids have been associated with mucosal damage and ulceration, partly attributed to their inhibitory effects on prostaglandin production and suppression of immune responses [14]. Additionally, certain chemotherapeutic agents and immunosuppressants may elicit mucosal injury, predisposing to ulcer formation and gastrointestinal bleeding [15].

Alteration of Gastrointestinal Motility and Blood Flow: Polypharmacy can disrupt gastrointestinal motility and blood flow, thereby affecting nutrient absorption, gastric emptying, and intestinal transit. Medications with anticholinergic properties, such as antipsychotics, tricyclic antidepressants, and antispasmodics, may impair gastrointestinal motility and exacerbate symptoms of constipation or gastroparesis [16]. Conversely, stimulant laxatives, used to alleviate constipation, may accelerate gastrointestinal transit and predispose to diarrhea or faecal incontinence. Moreover, vasoactive medications, including alpha-adrenergic agonists and calcium channel blockers, can modulate gastrointestinal blood flow, potentially contributing to mucosal ischemia and ulceration [17].

Influence of Polypharmacy on the gut Microbiota: The gut microbiota is essential for maintaining gastrointestinal balance, regulating the immune system, and supporting metabolic processes. Polypharmacy, especially the use of antibiotics, proton pump inhibitors, and immunosuppressants, can disrupt the composition and diversity of the gut microbiota, causing dysbiosis and microbial imbalance. Dysbiosis has been linked to several gastrointestinal disorders, such as inflammatory bowel disease, irritable bowel syndrome, and enteric infections, emphasizing the need to maintain microbial balance during polypharmacy [18].

METHODOLOGY:

Search Strategy: The present article used a systematic review and meta-analysis to examine the link between polypharmacy and enteric ulcers with various conditions, including GERD, IBD,NSAIDs, *H. pylori*.

The PRISMA guidelines were followed, and five electronic databases were searched for peer-reviewed articles published between 2000 to 2024 in English. A rigorous selection process was conducted to include higher quality and relevant studies for analysis.

Selection Process: The present study organized and managed a large number of publications for easy access and analysis. The papers were categorized based on their titles and abstracts into groups related to Polypharmacy and various conditions such as Enteric Ulcers, GERD, *H. pylori* and Cohort study. Various types of articles were identified, and those that were not relevant were excluded. The streamlined and comprehensive approach allowed for a thorough analysis of relevant literature for the present research paper **Fig. 1**.

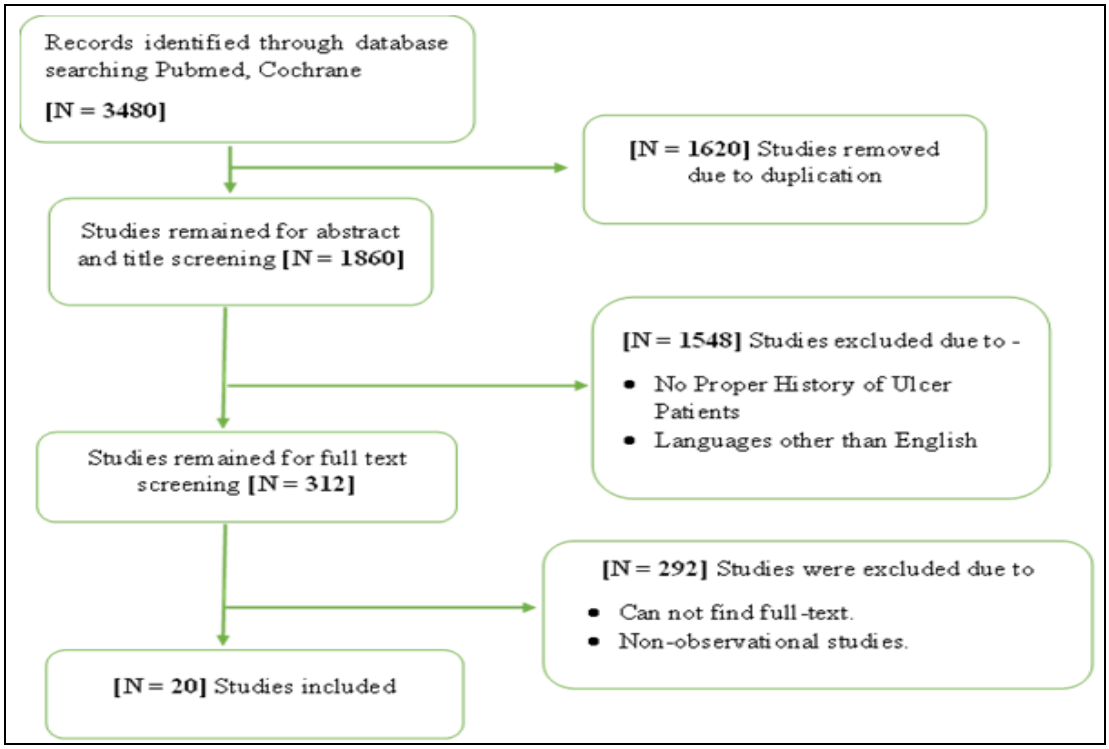

FIG. 1: FLOW DIAGRAM FOR THE SEARCH STRATEGY AND SELECTION PROCESS

Study Eligibility Criteria: The present study utilized the PICOS framework to establish eligibility criteria. It aimed to investigate corelation between polypharmacy and other gastrointestinal disorders to understand enteric ulcers. The population had no age restriction. The intervention/exposure was polypharmacy and other gastric disorders, with the comparison/control group consisting of subjects without such history. Only randomized controlled trials (RCTs) were selected to determine the eligibility of full-text papers for review.

Criteria for Inclusion:

- Age: All age groups were included.
- Studies in English language were included.
- Randomized control study was selected.
- Article includes Ulcers, GERD, IBD, NSAIDs, *H. pylori*.
- Full text articles were included.
- Articles published between the years 2000–2024 were included.

Criteria for Exclusion:

- Studies with animal population.
- Articles published before 2000 were excluded.
- Studies addressing adverse events or personality types were barred.
- Studies that examined genome/genetic allele studies.
- Studies that included autoimmune disorders.
- Only 20 articles were eligible for this effective survey study after qualification rules were used to short through the articles.

Evaluation of Study Quality: The systematic review regarded the caliber of the included studies as essential.It included only high quality RCTs. For assessing observational studies, the Newcastle-Ottawa Scale (NOS) was used, evaluating components such as study group selection, comparability, and outcome ascertainment. Standardized tools such as NOS ensured a transparent and systematic assessment of study quality.

Data Extraction: Data extraction is a crucial step in the research process, that involves gathering important details from eligible studies, such as study information, participant details, research questions, methodology, and outcome assessment. Following established procedures such as PRISMA

ensures systematic and effective analysis of data for drawing conclusions.

Data Analysis: Data extraction involves collecting relevant information from eligible studies. Mean change values or post-intervention values with standard deviations were calculated for each outcome for meta-analysis. Odds ratios (OR) and risk ratios (RR) were employed for data measured on identical scales. Study heterogeneity was evaluated using the I^2 test. A fixed-effect model was applied when heterogeneity was low ($I^2 \leq 50$), while a random effects model was utilized for moderate-to-high heterogeneity ($I^2 \geq 50$).

Risk of Publication: Publication bias risk was evaluated with at least 10 studies. Visual analysis of funnel plots was conducted, considering symmetrical plots as indicative of low publication bias risk and asymmetrical plots as indicative of high publication bias risk.

Statistical Analysis: In meta-analysis, researchers select between fixed-effect and random-effects models when conducting observational studies. Fixed-effect models assume consistent underlying influence across studies, while random-effects models consider varying effects. Random-effects models address heterogeneity and give more weight to smaller studies, leading to wider confidence intervals. If no heterogeneity exists, both models yield similar results.

Random-Effects Meta-Analysis: In a random-effects meta-analysis, it was presumed that the estimated treatment effect observed in trials might differ due to both sampling variability and actual variations in the treatment effect.

Reporting Bias: Reporting biases arise when the nature and direction of outcomes influence study findings. Positive and statistically significant results tend to be reported more frequently, particularly if they are published swiftly, in English, in prestigious journals, and cited by other researchers.

RESULTS:

Study Selection: A total of 3480 records were found through online literature searches. After reviewing 1860 relevant abstracts and removing duplicates, 3466 studies were considered pertinent. From these, 312 studies were further reviewed as they were classified as RCTs. Finally, 20 RCTs were included in the systematic analysis to assess the impact of family history on subjects with polypharmacy and enteric ulcers. These 20 articles were selected to reduce reporting bias.

Study Characteristics: The 20 included study characteristics are compiled in the flow diagram shown in **Fig. 4.** The total subjects included in each trial ranged from 70 to 550. The total number of subjects included in the present study was 6209, that included subjects with polypharmacy along with other comorbid conditions (such as multiple diseases like diabetes, arthritis, renal failure etc) The primary evaluation techniques employed in the studies focusing on polypharmacy and enteric ulcers revolved around two well-known diagnostic methods in the field of gastric health are endoscopic examination and histopathological analysis. These diagnostic approaches are fundamental for categorizing and diagnosing a range of gastric disorders.

Study Quality: A tool for assessing the calibre of randomized research for observational type of study including meta-analyses is the Newcastle Ottawa Scale (NOS). It is a tool used to assess the quality in systematic reviews and meta-analysis. The average score was found to be 5.71 which is considered as a good study score.

Statistical Analysis:

Impact of Odd Ratio for Polypharmacy and Enteric Ulcers: The odds ratio (OR) serves as a measure of the strength and direction of the relationship between an exposure and an outcome in case-control studies or similar observational studies. In this instance, the OR was calculated as 0.37 with a 95% confidence interval (CI) of 0.33 to 0.42. The level of heterogeneity within the group was relatively moderate ($\chi 2=20.97$, df=19, $P=0.34$; $I^2=9\%$). The overall effect test yielded a Z-score of 16.44 ($P<0.00001$). The confidence interval (CI) associated with the OR was crucial for evaluating the precision and statistical significance of the estimate. Since the CI does not include the value of 1.0, it indicates that the association is statistically significant, thereby reinforcing the evidence for the reduced odds suggested by the OR of 0.37 **Fig. 2**.

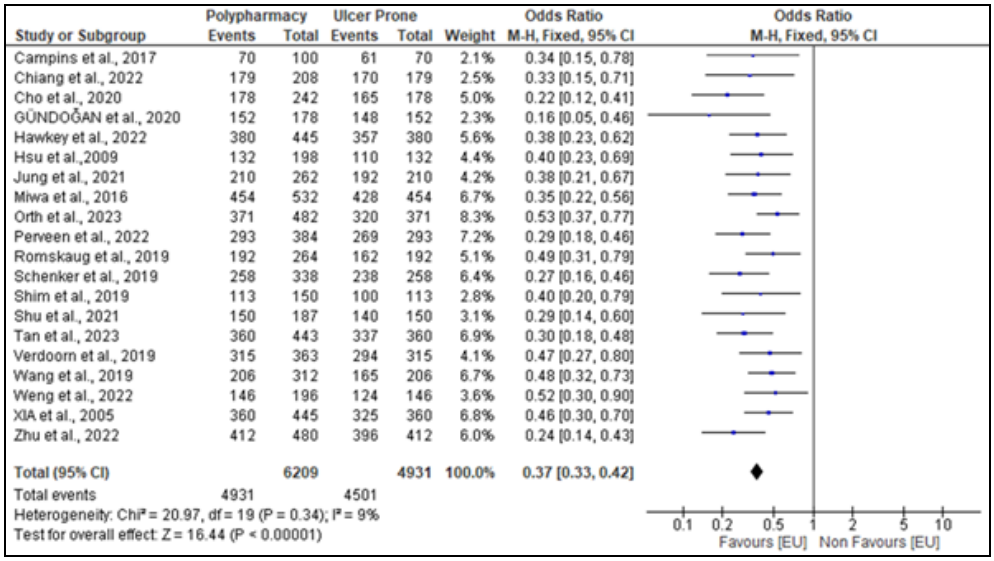

FIG. 2: FOREST PLOT OF ODDS RATIO

Risk of Publication Bias of Odds Ratio using Funnel Plot: Studies here with larger sample sizes or higher precision form a narrower cluster at the tip of the funnel hence there was no publication bias found as per the funnel plot given in **Fig. 3** while comparing the exposure and outcomes to evaluate the odds between the subjects **Fig. 3**.

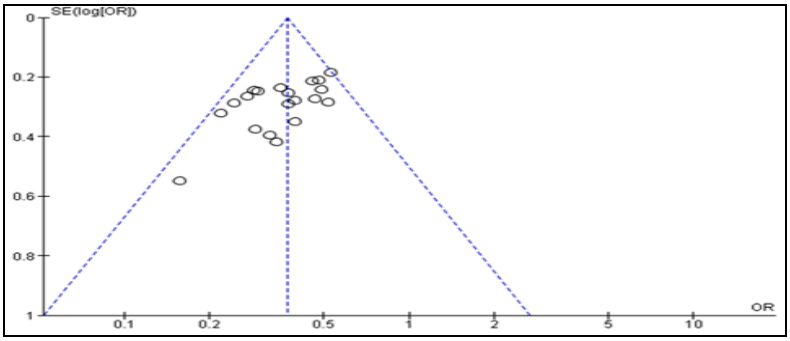

FIG. 3: FUNNEL PLOT OF ODDS RATIO

Impact of Risk Ratio for Polypharmacy and Enteric Ulcers: In this observational study, the risk ratio (RR) indicating the relationship between exposure and outcome was calculated as 0.87, with a 95% confidence interval (CI) [0.86, 0.89].

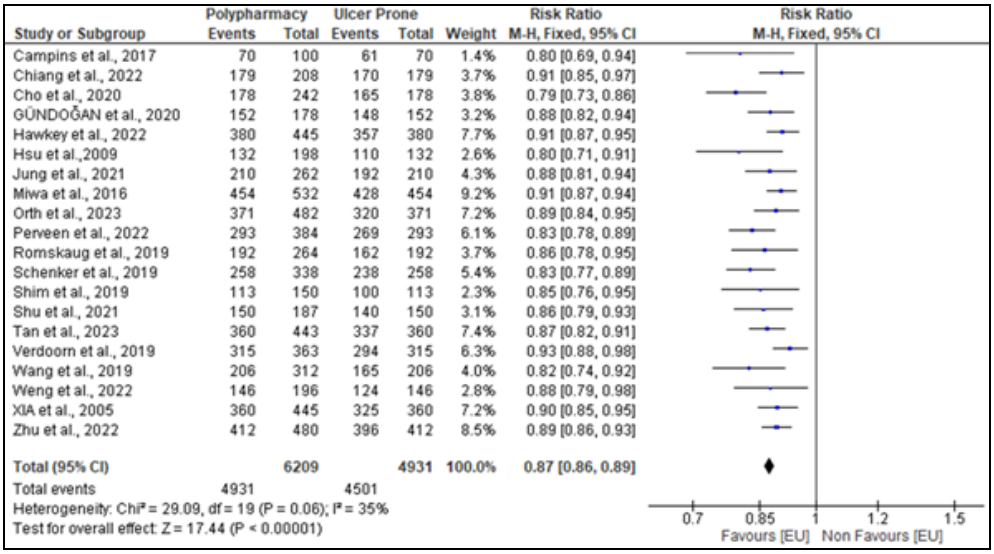

FIG. 4: FOREST PLOT OF RISK RATIO

There was moderate heterogeneity (I^2 = 35%) among the studies, but the overall effect was statistically significant (Z=17.44, *P*<0.00001). The CI not including the value 1.0 indicates that the association is statistically significant, supporting the reduced odds suggested by the RR of 0.87 **Fig. 4**.

Risk of Publication Bias of Risk Ratio using Funnel Plot: Studies here with larger sample sizes or higher precision form a narrower cluster at the tip of the funnel hence there was no publication bias found as per the funnel plot given in **Fig. 5** while comparing the exposure and outcomes to evaluate the risk between the subject **Fig. 5**.

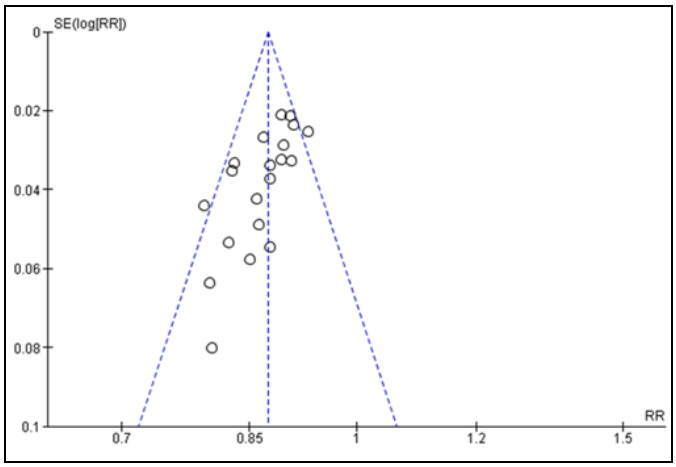

FIG. 5: FUNNEL PLOT OF RISK RATIO

DISCUSSION: The outcomes derived from this longitudinal investigation substantially augment our comprehension of the nexus between polypharmacy and the emergence of enteric ulcers. Employing rigorous methodologies in data procurement and analysis, our study has unearthed compelling evidence hinting at a plausible correlation between these two variables [19].

Polypharmacy, denoting the concurrent utilization of numerous pharmaceutical agents by an individual, has witnessed a surge in healthcare practice. This surge is propelled by advancements in medical science, which have ushered in a plethora of therapeutic modalities targeting diverse health conditions. Nonetheless, while polypharmacy may be imperative for managing intricate medical profiles or multiple concurrent ailments, it harbours inherent risks, notably the potential for adverse drug interactions and medication-related complications [20].

Our inquiry aimed to scrutinize the interrelation between polypharmacy and the incidence of enteric ulcers, concentrating on a cohort exhibiting varied medication consumption patterns. Our findings signify that individuals subjected to polypharmacy confront an escalated susceptibility to develop enteric ulcers vis-à-vis those with limited medication usage [21]. This association persisted significantly post adjustment for plausible confounding variables, encompassing age, gender, and underlying medical conditions [22].

Polypharmacy heightens the probability of drug interactions, which could perturb the delicate equilibrium of the gastrointestinal mucosal milieu, predisposing individuals to ulcerogenesis [23]. Furthermore, specific medications commonly integrated into polypharmacy regimens, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are acknowledged for their propensity to induce gastrointestinal mucosal injury and ulcer formation [24].

The findings of this study carry significant implications for both research and clinical applicationswhich was stated for OR 0.37[0.33,0.42] is [Chi^2=20.97, df=19 (*P*=0.34); I^2=9%]. Test for overall effect: Z=16.44 (*P*<0.00001) and for RR 0.87[0.86,0.89] is [Chi^2=29.06, df=19 (*P*=0.06); I^2=35%]. Test for overall effect Z=17.44 (*P*<0.00001). Understanding the relationship between polypharmacy and enteric ulcers can help identify potential targets for therapeutic interventions [25]. The shared underlying mechanisms suggest that therapeutic developments for one gastric disorder may have implications for other related disorders as well. This highlights the importance of interdisciplinary collaboration and knowledge exchange between different fields of study [25, 26].

However, it's important to take into account several findings when interpreting the results of this study. Firstly, the search strategy was limited to articles published in English between 2000 to 2024, which may introduce language and publication bias. Secondly, the included studies varied in design, sample size, and quality, which could affect the overall conclusions [27]. Moreover, the study did not take into account additional potential confounding variables like environmental exposures or

epigenetic modifications, which may influence the relationship between polypharmacy and enteric ulcers. The systematic review and meta-analysis presented in this study aimed to explore the potential correlation between polypharmacy and enteric ulcers [28]. The study evaluated the existing literature to understand the risk of polypharmacy and its potential association with various gastrointestinal disorders such as chronic liver disease, chronic kidney disease, and Zollinger-Ellison syndrome and others [29]. The discussion will focus on the findings, clinical significance, limitations of the study, and directions for future research.

The systematic review and meta-analysis of the eligible studies yielded valuable insights into the potential relationship between polypharmacy and enteric ulcers. The review identified several relevant articles that examined the coaggregation of these conditions within subjects. The data extracted from these studies suggested a potential co-relation for both polypharmacy and enteric ulcers.

Limitations: Cohort studies face biases like selection and loss to follow-up, impacting validity. Data quality depends on medical records and patient reports, prone to misclassification and recall biases. Unmeasured variables may confound results despite adjustments. Limited generalizability and inconsistent definitions/methods pose challenges. Longer follow-ups improve rare event detection but heighten loss to follow-up risk. Statistical power limitations require cautious interpretation, indicating the need for refined research.

CONCLUSION: In examining polypharmacy and enteric ulcers, we've found a strong link, emphasizing the need for careful medication management. Healthcare providers should assess the necessity and suitability of each medication to reduce the risk of ulcers. Further research should focus on understanding the connection better and developing interventions to minimize this risk. Addressing polypharmacy complexities can improve patient outcomes and enhance clinical care.

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