Creation of a score to predict risk of high conscious sedation requirements in patients undergoing endoscopy

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Background and Aims: The administration of intravenous conscious sedation to patients undergoing GI endoscopy carries a risk of cardiopulmonary adverse events. Our study aim was to create a score that stratifies the risk of occurrence of either high-dose conscious sedation requirements or a failed procedure.

Methods: Patients receiving endoscopy via endoscopist-directed conscious sedation were included. The primary outcome was occurrence of sedation failure, which was defined as one of the following: (1) high-dose sedation, (2) the need for benzodiazepine/narcotic reversal agents, (3) nurse-documented poor patient tolerance to the procedure, or (4) aborted procedure. High-dose sedation was defined as >10 mg of midazolam and/or >200 μg of fentanyl or the meperidine equivalent. Patients with sedation failure (n = 488) were matched to controls (n = 976) without a sedation failure by endoscopist and endoscopy date.

Results: Significant associations with sedation failure were identified for age, sex, nonclonazepam benzodiazepine use, opioid use, and procedure type (EGD, colonoscopy, or both). Based on these 5 variables, we created the high conscious sedation requirements (HCSR) score, which predicted the risk of sedation failure with an area under the curve of 0.70. Compared with the patients with a risk score of 0, risk of a sedation failure was highest for patients with a score ≥3.5 (odds ratio, 17.31; $P = 2 \times 10^{-14}$). Estimated area under the curve of the HCSR score was 0.68 (95% confidence interval, 0.63-0.72) in a validation series of 250 cases and 250 controls.

Conclusions: The HCSR risk score, based on 5 key patient and procedure characteristics, can function as a useful tool for physicians when discussing sedation options with patients before endoscopy. (Gastrointest Endosc 2020;91:595-605.)

INTRODUCTION

The use of GI endoscopy continues to increase worldwide, with approximately 51.5 million procedures performed in the United States in 2017 and estimated to increase at a rate of 2.6% annually.[1] Most endoscopies in the United States are performed with some type of sedation, and the percentage of those procedures performed with monitored anesthesia care (MAC) is increasing.[2] Nevertheless, 52.4% of all Medicare patients who underwent GI endoscopy in 2013 still did so without the use of MAC, and the most common sedative used in endoscopy remains midazolam, confirming

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval; CS, conscious sedation; HCSR, high conscious sedation requirements; MAC, monitored anesthesia care; OR, odds ratio.

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that endoscopist-directed conscious sedation (CS) is still a common and cost-effective option for sedation in GI endoscopy.[3,4] Options for sedation and analgesia in GI endoscopy are varied but may be influenced by locally available resources, provider expertise, and/or patient comorbidities. Choosing the best option for each patient requires a review of many factors, including previous tolerance to sedation, home medications, and medical comorbidities. Patients are routinely directed to either standard CS using a combination of an opiate (fentanyl or meperidine) and a benzodiazepine (midazolam) or MAC, typically with propofol and other sedatives. Determination of the correct dosing of analgesia and sedation during GI endoscopy can be a challenge. Ineffective sedation during GI endoscopy can be a demoralizing experience for both patients and endoscopists, but increasing doses of opiates and benzodiazepines are associated with higher frequencies of respiratory adverse events. [5,6] These patients often require repeated procedures, subjecting them again to the standard risks, affecting patient satisfaction, and causing frustration for practitioners. The decision to recommend standard CS or MAC is a clinical one that must include taking a thorough history and a physical examination.

Factors that commonly have an impact on directing patients toward MAC versus CS at our center include patient age, home use of opioid or benzodiazepine medications, body mass index (BMI), a history of poor tolerance for procedural sedation or previous anesthesia adverse event, history of a difficult airway, moderate to severe cardiopulmonary disease, untreated obstructive sleep apnea, home oxygen use, and/or significant limitations in exercise tolerance. There are data to suggest that a significant portion of patients with obstructive sleep apnea are unaware of this diagnosis and screen positively before undergoing endoscopy. This subset of patients is at high risk for sedation-related events.[7] In our institution, the ordering provider performs the first-line screening for sleep apnea during a mandatory pre-endoscopy examination. The endoscopy ordering set guides the provider in selecting the most appropriate type of sedation based on a number of variables, including untreated sleep apnea. Finally, the gastroenterology team reviews every order and gives feedback to the ordering provider before the procedure if MAC is deemed more appropriate than CS. Ultimately, selection of the most-appropriate GI endoscopy sedation option is at the discretion of the endoscopist on a case-by-case basis, with many decisions made based on gut feelings or previous personal experiences. Ideally, such decisions should be based on preprocedure patient-specific factors that guide the ordering provider to the most appropriate pathway for each individual.[8,9] Unfortunately, the decision to direct a patient away from standard CS and toward MAC has been demonstrated to be only weakly associated with patient factors, and more commonly be a function of facility-related variables.[10] A data-driven approach that focuses on clinical variables is needed to make accurate and cost-effective decisions regarding sedation and analgesia.

We aimed to identify certain pre-GI endoscopy patient-specific characteristics that are independently associated with high conscious sedation requirements (HCSRs) and create a risk score based on those variables to predict the likelihood of HCSRs in patients undergoing routine endoscopy.

METHODS

Study participants and data collection

All patients who underwent outpatient EGD, colonoscopy, or both using endoscopist-directed CS at the Mayo Clinic in Jacksonville, Florida, between November 2011 and May 2017 were considered for inclusion in this retrospective case-control study. Specifically, the study population represents patients undergoing nonemergent, elective procedures in our ambulatory endoscopy suites for diagnostic and/or therapeutic indications. In total, 52,881 GI endoscopies (33,070 colonoscopies and 19,811 upper endoscopies) were performed at Mayo Clinic Florida during the study period. All GI endoscopies were performed by 1 of 26 board-certified staff gastroenterologists practicing at our facility. Patients who met at least 1 of the criteria for HCSRs (ie, the cases) were matched in a 1:2 fashion based on the specific endoscopist and date of endoscopy (±180 days) with patients from the same sample who did not have HCSRs (ie, the controls). A case-control study design was chosen instead of a cohort study design because of the relatively rare nature of the HCSR outcome that defines case-control status. In total, 488 cases with HCSRs and the 976 controls without HCSRs were included.

Sedation-related information was collected regarding intraprocedural midazolam doses, intraprocedural fentanyl doses, intraprocedural meperidine doses, intraprocedural diphenhydramine doses, intraprocedural promethazine doses, incomplete procedures, poor procedure tolerance, reversal agents used, and aborted procedures. Information regarding patient and endoscopy characteristics collected for potential inclusion in our risk score included age, race, sex, BMI, MELD (Model for End-Stage Liver Disease) score, history of sleep apnea, history of colon resection, history of small-bowel resection, current alcohol use, current tobacco use, current medication use (benzodiazepines, opioids, selective serotonin or norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory drugs, antiepileptic drugs, tricyclic antidepressants, antipsychotics, medications for restless leg syndrome, magnesium, iron sulfate, proton pump inhibitors, attention-deficit hyperactivity disorder medications, diabetic medications), procedure type (EGD, colonoscopy, or both EGD and colonoscopy), and whether the endoscopy was performed with a fellow. As a retrospective study, all data were retrieved from the electronic health record at our institution; "current use of medications" refers to the medications listed in the patients' electronic health record

TABLE 1. Sedation-related information for cases (patients with high conscious sedation requirements) and controls (patients without high conscious sedation requirements)

Variable	Controls (n = 976)	Cases (n = 488)
Midazolam >10 mg	0 (0.0)	163 (33.4)
Fentanyl >200 μg	0 (0.0)	199 (40.8)
Meperidine >100 mg	0 (0.0)	46 (9.4)
Incomplete procedure	0 (0.0)	7 (1.4)
Poor tolerance (nursing documentation)	0 (0.0)	300 (61.5)
Reversal agent needed	0 (0.0)	7 (1.4)
Aborted procedure	0 (0.0)	140 (28.7)
Received fentanyl	860 (88.1)	419 (85.9)
Dose of fentanyl (μg)	150 (25, 200)	200 (15, 550)
Received midazolam	971 (99.5)	482 (98.8)
Dose of midazolam (mg)	7 (1, 10)	10 (2, 200)
Received meperidine	129 (13.2)	77 (15.8)
Dose of meperidine (mg)	75 (38, 100)	125 (10, 300)
Received diphenhydramine	90 (9.2)	204 (41.8)
Dose of diphenhydramine (mg)	50 (25, 50)	50 (13, 100)
Received promethazine	12 (1.2)	34 (7.0)
Dose of promethazine (mg)	25 (13, 25)	25 (12, 50)

Values are number (%) except where indicated otherwise. The sample median (minimum, maximum) is given for continuous variables.

at the time of their GI endoscopy. This study was approved by the Mayo Clinic Institutional Review Board.

Validation series

To attempt to externally validate the score that was created to predict the risk of HCSRs, we also included a series of 250 cases with HCSRs and 250 controls without HCSRs from the Mayo Clinic in Rochester, Minnesota. Cases and controls were matched in a 1:1 fashion based on the specific endoscopist and date of endoscopy (±180 days). Inclusion criteria for the validation series was the same as for the original series of 488 cases and 976 controls. GI endoscopies were performed by 1 of 62 board-certified staff gastroenterologists.

Definition of the primary outcome

The primary outcome measure of the study was occurrence of HCSRs during GI endoscopy and was defined according to the 7 criteria listed in Table 1. Specifically, an HCSR was defined as the occurrence of one of the following: (1) dose of midazolam >10 mg, (2) dose of fentanyl >200 μg, (3) dose of meperidine >100 mg, (4) need for a reversal agent (either flumazenil or naloxone), (5) incomplete procedure based on nursing documentation, (6) aborted procedure based on nursing documentation, or (7) poorly tolerated procedure based on nursing documentation. Although the nursing documentation was used in review to define the cases of incomplete or aborted procedures, the final determination was made by the staff endoscopist and documented in the nursing notes. Our Procedural Sedation Committee has stated that 5 mg of midazolam, 100 μg of fentanyl, and 100 mg of meperidine are appropriate target doses for CS at our institution. The criteria defining medication doses are based on a consensus definition from the endoscopists practicing at our institution and reflect twice the recommended doses. The determination of a GI endoscopy as incomplete or aborted was made by the endoscopist and is most often reflective of perceived patient intolerance or dosing of CS that exceeds the comfort level of the provider. The notation of "poorly tolerated" was made by the endoscopy nurse and was based on a standard scoring system used at our institution. Endoscopy nurses were instructed to rate each patient's tolerance as a reflection of whether the patient was uncomfortable or complained of pain during the procedure. This scoring system assigns 1 of 4 possible assessments that range from "tolerated well" to "poorly tolerated." Scoring of each patient occurs after the GI endoscopy is complete and takes into account the cumulative perceived discomfort over the course of the entire sedation event. "Poorly tolerated" denotes that the nurse deemed the patient to be uncomfortable more than 75% of the time during GI endoscopy.

Statistical analysis

Continuous variables were summarized using the sample median and range. Categorical variables were summarized as the number and percentage of patients. In the original series of 488 cases and 976 controls, associations of patient and procedure characteristics with occurrence of HCSRs were evaluated using single-variable and multivariable logistic regression models. Single-variable models were adjusted only for whether the endoscopy was performed with a fellow to eliminate any confounding influence this variable may have. As a teaching institution, our staff gastroenterologists perform many endoscopic procedures with trainees. The percentage of endoscopic procedures in which a fellow participated was 14.1% at Mayo Clinic Florida and 27% at Mayo Clinic Rochester during the study period. There are 2 reasons we chose to adjust for this variable: (1) endoscopy procedures that involve a fellow often take more time to complete than those that do not; (2) it is not always known at the pre-endoscopic evaluation whether any procedure will involve a fellow, and we want this model to be applicable in the pre-endoscopic context. Multivariable models were adjusted for whether the endoscopy was performed with a fellow, as well as all variables that were associated with occurrence of HCSRs with a P value <.20 in single-variable analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated and correspond to the multiplicative increase in odds of occurrence of HCSRs. Based on the results of the multivariable logistic regression analysis, we

created a risk score for HCSRs as follows. First, only those variables that were associated with occurrence of HCSRs with a P value <.05 were included in the risk score (excluding whether the procedure was performed with a fellow because this information could not be used for pre-endoscopy prognostic purposes). For these variables, the reference category was assigned a score of 0, and any categories that did not differ from the reference category with a P value <.05 were also assigned a score of 0. For other categories that did differ from the reference category of the given variable with a P value <.05, scores were assigned by taking the regression coefficient (ie, the natural logarithm of the OR) and rounding it to the nearest 0.5.[11] The individual scores for each of these variables were then summed to create an HCSR risk score for each patient. We calculated the proportion of patients with HCSRs at each level of the HCSR risk score to assess the overall effectiveness of the score in discriminating between patients with and without HCSRs; however, these proportions were severely biased as a result of the 1:2 matched case/control study design (the same is true for the 1:1 case/control design of the validation series). Therefore, we used Bayes' theorem to estimate what these proportions would be in the overall endoscopy patient population at our institution, assuming that the true proportion of patients with HCSRs in this population is 2.5%, which is an estimate based on past clinical experience at our institution. Given that this estimate of 2.5% may not be applicable for other institutions, we also performed similar calculations assuming that the true proportion of patients with HCSRs is 1%, 5%, and 10%. Importantly, the ORs, 95% CIs, and P values that were obtained from logistic regression analysis and subsequently used to create the HCSR risk score are not biased as a result of the 1:2 matched case/control design.

We performed both internal and external validation of the HCSR risk score. For the internal validation, we used a bootstrap approach to avoid obtaining an overly optimistic estimate regarding the ability of the HCSR risk score to predict HCSRs (as measured by area under the receiver operating characteristic curve [AUC]).[11] Specifically, after estimating the AUC of the HCSR risk score in the original sample that was used to develop it, we generated 200 bootstrap samples where matched case/control trios were sampled with replacement. In each bootstrap sample, we applied the same modeling strategy that was used to obtain the HCSR risk score to obtain a new risk score. The AUC was then estimated for this new risk score in both the bootstrap sample and the original sample, and the "optimism" was then calculated as the difference in AUCs between the bootstrap and original sample. The median of these optimism values was then subtracted from the AUC that was estimated from the original sample to obtain an optimism-corrected AUC. This optimism-corrected AUC provides a realistic estimate of the true prediction accuracy that takes into account the fact that the HCSR risk score was created based on an ideal performance in the data from which it was generated, and therefore may have a less ideal performance in an independent series of patients. In addition, we assessed the calibration of the HCSR risk score by comparing the predicted proportion of patients with HCSRs from logistic regression analysis including HCSRs as a covariate with the actual proportion of patients with HCSRs; these 2 quantities were plotted against one another in a calibration plot. For external validation, we assessed the ability of the HCSR risk score to predict HCSRs in the validation series by estimating the AUC. P values of $\leq$.05 were considered as statistically significant. All statistical tests were 2-sided. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc, Cary, NC, USA).

RESULTS

Sedation-related information is shown in Table 1 for the 488 cases with HCSRs and the 976 controls without HCSRs; patient and procedure characteristics are summarized in Table 2. A higher frequency of home benzodiazepine use was noted in patients with HCSRs compared with those without HCSRs (25.0% vs 14.1%; Table 2). When reviewing non-rare specific home benzodiazepines, only clonazepam use was not seen more frequently in the patients with HCSRs (3.7% vs 3.6%; Supplementary Table 1, available online at www.giejournal.org). Therefore, we created a variable for use of nonclonazepam benzodiazepines (Table 2), and given that this alternative variable was more strongly associated with risk of HCSRs than use of any benzodiazepines (data not shown), we retained nonclonazepam benzodiazepines as a variable for potential inclusion in our risk score and did not evaluate use of "any benzodiazepines" in further analyses. Opioid use was also much more frequent in the patients with HCSRs in the descriptive analysis (21.2% vs 12.3%; Table 2, available online at www.giejournal.org), however, further examination of specific opioid types revealed no consistently higher frequencies among the cases for opioids that were used most commonly (Supplementary Table 1), and therefore we did not alter this opioid use variable in subsequent analyses.

An evaluation of associations of patient-specific and procedure characteristics with risk of HCSRs is shown in Table 3. In single-variable analysis that was adjusted only for whether the endoscopy was performed with a fellow, significant associations with HCSRs were observed for age ($P = 4 \times 10^{-24}$), sex ($P = .0003$), BMI ($P = .031$), current tobacco use ($P = .006$), use of non-clonazepam benzodiazepines ($P = 3 \times 10^{-8}$), use of opioids ($P = 1 \times 10^{-5}$), use of serotonin or norepinephrine reuptake inhibitors ($P = .039$), use of tricyclic antidepressants ($P = .015$), use of antipsychotics ($P = .004$), use of magnesium

TABLE 2. Patient and procedure characteristics for cases (patients with high conscious sedation requirements) and controls (patients without high conscious sedation requirements)

Variable	Controls (n = 976)	Cases (n = 488)
Age	60.7 (17.2, 91.5)	50.8 (16.3, 86.7)
≤30.00 years	36 (3.7)	77 (15.8)
30.01-40.00 years	57 (5.8)	52 (10.7)
40.01-50.00 years	133 (13.6)	99 (20.3)
50.01-60.00 years	241 (24.7)	131 (26.8)
60.01-70.00 years	319 (32.7)	89 (18.2)
>70.00 years	190 (19.5)	40 (8.2)
Race (non-white)	117 (12.0)	48 (9.8)
Sex (female)	519 (53.2)	308 (63.1)
Body mass index	27.7 (16.7, 61.2)	27.4 (13.4, 65.1)
≤25.00 kg/m^2	294 (30.5)	151 (31.1)
25.01-30.00 kg/m^2	357 (37.1)	152 (31.3)
30.01-35.00 kg/m^2	193 (20.0)	97 (20.0)
> 35.00 kg/m^2	119 (12.4)	86 (17.7)
MELD score	6 (6, 30)	6 (6, 27)
≤6	843 (86.4)	432 (88.7)
7-14	90 (9.2)	34 (7.0)
≥15	43 (4.4)	21 (4.3)
History of sleep apnea	80 (8.2)	36 (7.4)
History of colon resection	23 (2.4)	14 (2.9)
History of small-bowel resection	27 (2.8)	10 (2.0)
Current alcohol use	542 (55.5)	267 (54.8)
Current tobacco use	87 (8.9)	67 (13.7)
Current medication use		
Benzodiazepines	138 (14.1)	122 (25.0)
Benzodiazepines (excluding clonazepam)	103 (10.6)	104 (21.3)
Opioids	120 (12.3)	103 (21.1)
Serotonin or norepinephrine reuptake inhibitors	168 (17.2)	106 (21.7)
Nonsteroidal anti-inflammatory drugs	311 (31.9)	128 (26.2)
Antiepileptic drugs	62 (6.4)	36 (7.4)
Tricyclic antidepressants	25 (2.6)	25 (5.1)
Antipsychotics	9 (0.9)	15 (3.1)
Restless leg syndrome medications	7 (0.7)	5 (1.0)
Magnesium	37 (3.8)	9 (1.8)
Iron sulfate	42 (4.3)	20 (4.1)
Proton pump inhibitors	389 (39.9)	207 (42.4)
Attention-deficit hyperactivity disorder medications	11 (1.1)	14 (2.9)
Diabetes medications	99 (10.1)	37 (7.6)
Procedure type		
EGD	326 (33.4)	151 (30.9)
Colonoscopy	254 (26.0)	94 (19.3)
Both EGD and colonoscopy	396 (40.6)	243 (49.8)
Procedure performed with a fellow	124 (12.7)	80 (16.4)

Values are number (%) except where indicated otherwise. The sample median (minimum, maximum) is given for continuous variables. Information was unavailable regarding body mass index (13 controls and 2 cases), MELD score (1 case), and current use of alcohol (1 case).
MELD, Model for End-Stage Liver Disease.

TABLE 3. Associations of patient and procedure characteristics with high conscious sedation requirements

Variable	Single-variable analysis		Multivariable analysis	
	Odds ratio (95% confidence interval)	*P* value	Odds ratio (95% confidence interval)	*P* value
Age	Overall test of difference: $P = 4 \times 10^{-24}$		Overall test of difference: $P = 2 \times 10^{-21}$	
>70 years	1.00 (reference)	N/A	1.00 (reference)	N/A
60.01-70.00 years	1.33 (0.88-2.01)	.18	1.33 (0.86-2.04)	.20
50.01-60.00 years	2.62 (1.75-3.92)	3×10^{-6}	2.56 (1.68-3.89)	1×10^{-5}
40.01-50.00 years	3.56 (2.32-5.48)	7×10^{-9}	3.41 (2.16-5.38)	1×10^{-7}
30.01-40.00 years	4.45 (2.67-7.40)	9×10^{-9}	4.82 (2.78-8.34)	2×10^{-8}
≤30 years	10.19 (6.04-17.19)	3×10^{-18}	11.30 (6.44-19.83)	3×10^{-17}
Race (non-white)	0.82 (0.57-1.16)	.26	0.77 (0.52-1.14)	.19
Sex (Female)	1.49 (1.20-1.89)	.0003	1.30 (1.00-1.67)	.046
Body mass index	Overall test of difference: $P = .031$		Overall test of difference: $P = .22$	
≤25.00 kg/m^2	1.00 (reference)	N/A	1.00 (reference)	N/A
25.01-30.00 kg/m^2	0.84 (0.64-1.10)	.21	1.16 (0.85-1.58)	.35
30.01-35.00 kg/m^2	0.98 (0.72-1.35)	.92	1.25 (0.88-1.79)	.22
>35.00 kg/m^2	1.40 (0.99-1.96)	.054	1.49 (1.02-2.18)	.039
MELD score	Overall test of difference: $P = .37$		Overall test of difference: $P = .47$	
≤6	1.00 (reference)	N/A	1.00 (reference)	N/A
7-14	0.74 (0.49-1.12)	.16	0.97 (0.62-1.52)	.87
≥15	0.97 (0.57-1.65)	.90	1.42 (0.80-2.54)	.24
History of sleep apnea	0.90 (0.59-1.35)	.59	1.08 (0.68-1.70)	.77
History of colon resection	1.26 (0.64-2.47)	.50	1.44 (0.68-3.04)	.35
History of small-bowel resection	0.74 (0.36-1.55)	.43	0.58 (0.25-1.38)	.21
Current alcohol use	0.97 (0.78-1.20)	.75	1.16 (0.91-1.48)	.23
Current tobacco use	1.61 (1.15-2.26)	.006	1.29 (0.89-1.87)	.19
Current medication use				
Benzodiazepines (excluding clonazepam)	2.33 (1.73-3.14)	3×10^{-8}	2.24 (1.60-3.13)	3×10^{-6}
Opioids	1.92 (1.44-2.56)	1×10^{-5}	1.74 (1.26-2.40)	.0007
Serotonin or norepinephrine reuptake inhibitors	1.33 (1.02-1.75)	.039	1.02 (0.75-1.39)	.90
Nonsteroidal anti-inflammatory drugs	0.76 (0.60-0.97)	.028	0.98 (0.75-1.29)	.88
Antiepileptic drugs	1.17 (0.77-1.80)	.46	0.92 (0.57-1.47)	.72
Tricyclic antidepressants	2.02 (1.15-3.56)	.015	1.65 (0.87-3.14)	.12
Antipsychotics	3.43 (1.49-7.91)	.004	2.17 (0.84-5.60)	.11
Restless leg syndrome medications	1.42 (0.45-4.51)	.55	0.77 (0.23-2.61)	.68
Magnesium	0.47 (0.23-0.99)	.047	0.55 (0.25-1.22)	.14
Iron sulfate	0.94 (0.55-1.63)	.83	0.99 (0.55-1.78)	.96
Proton pump inhibitors	1.11 (0.89-1.38)	.36	1.18 (0.92-1.52)	.20
Attention-deficit hyperactivity disorder medications	2.68 (1.21-5.95)	.016	1.74 (0.72-4.18)	.22
Diabetes medications	0.73 (0.49-1.09)	.12	0.97 (0.63-1.50)	.90

(*continued on the next page*)

($P = .047$), use of attention-deficit hyperactivity disorder medications ($P = .016$), and procedure type ($P = .002$).

In the multivariable analysis adjusting for whether the endoscopy was performed with a fellow as well as any variable that was associated with HCSRs with a *P* value ≤.20 in the single-variable analysis, significant associations with HCSRs remained for age ($P = 2 \times 10^{-21}$), female sex (OR, 1.30; $P = .046$), nonclonazepam benzodiazepine

TABLE 3. Continued

Variable	Single-variable analysis		Multivariable analysis	
	Odds ratio (95% confidence interval)	*P* value	Odds ratio (95% confidence interval)	*P* value
Procedure type	Overall test of difference: .002		Overall test of difference: .002	
EGD	1.00 (reference)	N/A	1.00 (reference)	N/A
Colonoscopy	0.78 (0.58-1.07)	.12	1.04 (0.74-1.47)	.81
Both EGD and colonoscopy	1.30 (1.01-1.67)	.042	1.56 (1.18-2.07)	.002
Procedure performed with a fellow	1.35 (0.99-1.83)	.055	1.42 (1.01-1.99)	.041

Odds ratios, 95% confidence intervals, and *P* values result from logistic regression models where the outcome was high conscious sedation requirements. An odds ratio >1 indicates that the given characteristic is associated with a higher likelihood of high conscious sedation requirements, whereas an odds ratio <1 indicates that the given characteristic is associated with a lower likelihood of high conscious sedation requirements. Single-variable models were adjusted only for procedures performed with a fellow. Multivariable models were adjusted for procedures performed with a fellow and all variables that were associated with high conscious sedation requirements with $P < .20$ in single-variable analysis (age, sex, body mass index, procedure type, current tobacco use, benzodiazepines excluding clonazepam, opioids, serotonin or norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, antipsychotics, magnesium, attention-deficit hyperactivity disorder medications, and diabetic medications).

TABLE 4. High conscious sedation requirement risk score calculation

Variable	Individual score
Age	
>70 years	0
60.01 to 70.00 years	0
50.01 to 60.00 years	1
40.01 to 50 years	1
30.01 to 40 years	1.5
≤30 years	2.5
Sex	
Male	0
Female	0.5
Benzodiazepines (excluding clonazepam)	
No	0
Yes	1
Opioids	
No	0
Yes	0.5
Procedure type	
EGD	0
Colonoscopy	0
Both EGD and colonoscopy	0.5

For each of the 5 variables included in the risk score, the reference category was assigned a score of 0, and any categories that did not differ with the reference category in the multivariable analysis with a *P* value <.05 were also assigned a score of 0. For other categories that did differ from the reference category of the given variable with a *P* value <.05 in the multivariable analysis, scores were assigned by taking the regression coefficient (ie, the natural logarithm of the odds ratio) from the multivariable analysis and rounding it to the nearest 0.5. The individual scores for each of these variables were then summed to create an high conscious sedation requirement risk score (which has a possible range of 0 to 5) for each patient.

use (OR, 2.24; $P = 3 \times 10^{-6}$), opioid use (OR, 1.74; $P = .0007$), and for patients undergoing both colonoscopy and EGD within the same sedation event ($P = .002$). More specifically, with regard to age, in a comparison with patients older than 70 years, the risk of HCSRs was higher for those between 50 and 60 years (OR, 2.56; $P = 1 \times 10^{-5}$), between 40 and 50 years (OR, 3.41; $P = 1 \times 10^{-7}$), between 30 and 40 years (OR, 4.82; $P = 2 \times 10^{-8}$), and ≤30 years (OR, 11.30; $P = 3 \times 10^{-17}$). For procedure type, compared with patients undergoing EGD alone, the risk of HCSRs was not different for patients undergoing colonoscopy alone (OR, 1.04; $P = .81$), but was significantly higher for those undergoing both EGD and colonoscopy (OR, 1.56; $P = .002$). Patient and procedure characteristics are shown in Supplementary Table 2 for those ≤30 years who were at especially high risk of HCSRs.

Based on the findings involving the 5 variables that were significantly associated with HCSRs in our multivariable logistic regression analysis, we created the HCSR risk score according to our previously described methodology (Table 4). The HCSR risk score ranges from 0 to 5 and predicts the risk of HCSRs with an optimism-corrected AUC equal to 0.70 on internal validation. Agreement between the predicted and actual proportions of patients with HCSRs was good (Fig. 1A).

As shown in Table 5, the proportion of patients with HCSRs in our study ranged from 14.1% (score = 0) to 73.9% (score = 3.5-5). However, these proportions are highly biased because 33% of the patients were cases in our 1:2 matched case-control design. When estimating what these proportions would be, assuming that the true proportion of patients with HCSRs is 2.5%, proportions ranged from 0.8% (score = 0) to 12.7% (score = 3.5-5); these calculations were also performed when assuming that the proportion of patients with HCSRs is 1%, 5%, and 10% (Supplementary Table 3, available online at www.giejournal.org). Compared with the patients with an HCSR risk score of 0, the risk of HCSR was slightly (but not significantly) higher for those with a risk score of 0.5 (OR, 1.36; $P = .31$), and significantly higher for patients with a risk score of 1 (OR, 1.84; $P = .038$), a risk score of 1.5 (OR, 2.89; $P = .0002$), a risk score of 2 (OR, 3.78; $P =$

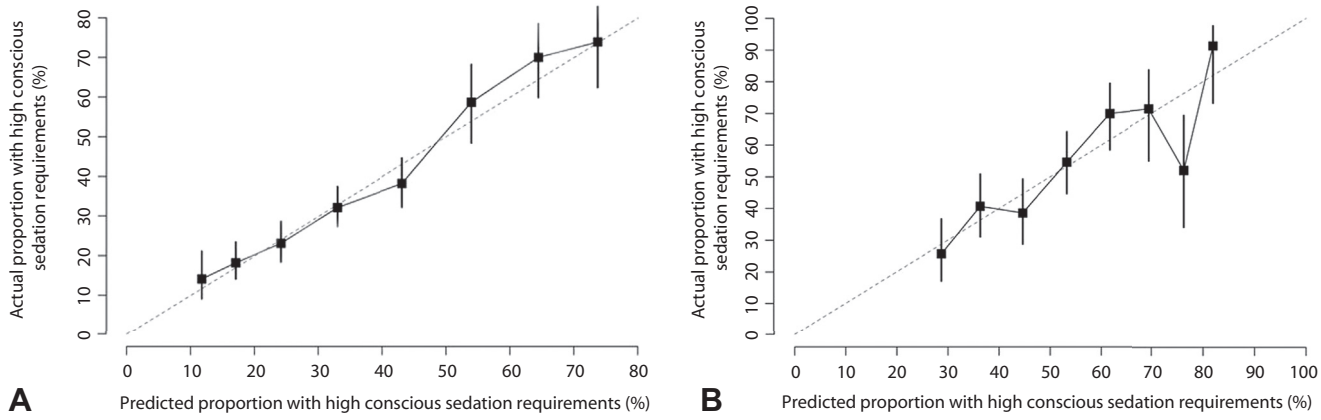

Figure 1. A, original series of 488 cases and 976 controls. **B,** validation series of 250 cases and 250 controls. Patients were grouped according to their HCSR risk score (0, 0.5, 1, 1.5, 2, 2.5, 3, or 3.5-5). The dashed line indicates the ideal reference line where the predicted proportion of patients with high conscious sedation requirements is equal to the observed proportions. Vertical lines represent the 95% CI for the given observed proportion of patients with high conscious sedation requirements.

4×10^{-6}), a risk score of 2.5 (OR, 8.68; $P = 6 \times 10^{-11}$), a risk score of 3 (OR, 14.26; $P = 9 \times 10^{-15}$), and a risk score of 3.5 or higher (OR, 17.31; $P = 2 \times 10^{-14}$). The HCSR risk score showed similar ability to predict the risk of HCSRs in the validation series of 250 cases and 250 controls, with an AUC equal to 0.68 (95% CI, 0.63-0.72; Table 5, Supplementary Table 3, Fig. 1B). Characteristics of the validation series are summarized in Supplementary Table 4 (available online at www.giejournal.org).

DISCUSSION

In recent years, the use of MAC for GI endoscopies has increased from about one-third in 2010 to nearly half of all cases in 2013.[4] Proponents of MAC highlight these changes as a function of increasing focus on patient satisfaction, the desire for increased efficiency, and the compensation structure of certain insurance policies that will reimburse for MAC but not endoscopist-directed CS.[12-14] In addition, a quicker onset of action, shorter half-life, and reduction in reported nausea and vomiting have encouraged a trend toward the use of propofol over the standard CS agents (benzodiazepines and opiates).[9,15-19] However, endoscopist-directed CS remains a common and appropriate option for many patients. Endoscopist-directed CS is less expensive and requires fewer ancillary staff. The use of MAC over endoscopist-directed propofol administration is estimated to cost the U.S. health care system an additional $3.2 billion over 10 years,[20] but outcome data do not conclusively support its use over CS.[12,14]

The context into which we introduce our findings is one that we believe demands a more objective evaluation of the patients we are targeting. Previous research suggests ordering providers' direction of patients to MAC is more often a product of facility-related and financial factors instead of patient-specific variables and has called for a more data-driven approach.[10,21] Clearly, certain patient populations require specific sedation strategies based on comorbid factors. Patients with celiac disease and cirrhosis, for example, may need higher doses of sedatives and/or analgesics to achieve the same effect.[22,23] Patient comfort and procedural tolerance is an important factor to consider in directing a patient toward or away from CS. It is important for the endoscopist to consider other methods to minimize pain during insertion, which include, but are not limited to, water immersion and exchange.[24-26] The desire to identify the difficult-to-sedate patient both in terms of safety and patient satisfaction has been the subject of previous research efforts.[27-35] Peña et al[30] developed a questionnaire to predict patient satisfaction and tolerance of endoscopic procedures. We built on these ideas and attempted to answer the call submitted by DeLegge more than 10 years ago that "a pre-procedure tool that would assign patients to the right endoscopic sedation regimen would be very useful in generating a positive patient experience. This tool would ideally be brief, easy to score, broadly applicable to a multitude of endoscopic procedures, and easy to interpret."[29]

Our findings indicate that preprocedure medication reconciliation is extremely important when selecting a sedation strategy for an individual patient. The use of nonclonazepam benzodiazepines showed a stronger association with risk of HCSRs than did use of prescription opioids. We also found that young age carried more weight than any other factor as a risk for difficult sedation. Patients ≤30 years of age were more likely to have HCSRs than those older than 60 years who took benzodiazepines or opioids or underwent both EGD and colonoscopy. We see these associations and their magnitudes as the most novel aspects of our research. Our work has focused on

TABLE 5. High conscious sedation requirements according to the high conscious sedation requirement risk score

	Association with HCSRs							
	Original series (488 cases, 976 controls)				Validation series (250 cases, 250 controls)			
HCSR risk score	Fraction (%) of patients with HCSRs in our case-control study*	Percentage of patients with HCSRs assuming that the true percentage of cases is 2.5%	Odds ratio (95% confidence interval)	*P* value	Fraction (%) of patients with HCSRs in our case-control study*	Percentage of patients with HCSRs assuming that the true percentage of cases is 2.5%*	Odds ratio (95% confidence interval)	*P* value
0	18/128 (14.1)	0.8	1.00 (reference)	N/A	19/74 (25.7)	0.9	1.00 (reference)	N/A
0.5	48/264 (18.2)	1.1	1.36 (0.75-2.45)	.31	37/91 (40.7)	1.7	1.98 (1.02-3.87)	.045
1	61/264 (23.1)	1.5	1.84 (1.03-3.26)	.038	32/83 (38.6)	1.6	1.82 (0.92-3.60)	.087
1.5	104/324 (32.1)	2.4	2.89 (1.67-5.01)	.0002	53/97 (54.6)	3.0	3.49 (1.81-6.73)	.0002
2	89/233 (38.2)	3.1	3.78 (2.15-6.64)	4×10^{-6}	49/70 (70.0)	5.6	6.75 (3.25-14.02)	3×10^{-6}
2.5	54/92 (58.7)	6.8	8.68 (4.54-16.61)	6×10^{-11}	25/35 (71.4)	6.0	7.24 (2.94-17.80)	2×10^{-5}
3	63/90 (70.0)	10.7	14.26 (7.28-27.92)	9×10^{-15}	14/27 (51.9)	2.7	3.12 (1.25-7.80)	.015
3.5 to 5	51/69 (73.9)	12.7	17.31 (8.32-36.03)	2×10^{-14}	21/23 (91.3)	21.2	30.39 (6.51-141.91)	1×10^{-5}

Odds ratios, 95% confidence intervals, and *P* values result from an unadjusted logistic regression model. The HCSR risk score predicted the occurrence of HCSRs with an optimism-corrected area under the receiver operating characteristic curve of 0.70 in the original series and 0.68 in the validation series.

HCSR, High conscious sedation requirement.

*The proportion of patients with HCSRs at each level of the HCSR risk score was estimated for the patients in our case-control study to assess the overall effectiveness of the score in discriminating between patients with and without HCSRs; however, these proportions are severely biased due to the 1:2 matched case-control study design (and the 1:1 matched design of the validation series). Therefore, we used Bayes' theorem to estimate what these proportions would be in the overall endoscopy patient population at our institution, assuming that the true proportion of patients with HCSRs is 2.5%.

isolating a select few variables that associate strongly and can be easily identified in the pre-endoscopic setting. We have endeavored to make our scoring system accurate, simple, and (ever more important in the modern age) quick to use.

The primary limitation of our study is its retrospective design and corresponding inherent impact on the data quality. We also recognize that other factors outside those included in the HCSR risk score, such as patient comorbidities and American Society of Anesthesiologists score, should influence the ordering provider's choice of sedation for GI endoscopy.[10,21] In addition, we would like to recognize the subjective nature of our definition of HCSRs (maximum doses of midazolam, fentanyl, and meperidine, use of a reversal agent, incomplete procedure, aborted procedure, and poor tolerance of procedure). Midazolam, fentanyl, and meperidine are the 3 medications used for inducing and maintaining sedation and analgesia in endoscopist-directed CS at our institution and were the only ones for which we established limits. Those limits are based on expert opinion of GI endoscopy providers at our institution and represent the minimum doses that we believe would have changed our pre-endoscopy decision making had they been known. The documentation of "poorly tolerated" is also a subjective variable, and one that makes up a large proportion of our cases (61.5%). First, many of these cases also met 1 of the other inclusion criteria. However, we acknowledge that poor tolerance alone does not necessarily make 1 patient more appropriate for MAC. Multiple factors such as pain, anxiety, and combativeness could all be interpreted as poor tolerance, making this variable admittedly subjective.

Informally, our authors estimate that we encounter a sedation failure in about 2.5% to 5% of our patients undergoing outpatient GI endoscopy with CS. As far as we have been able to ascertain, there are no good recent data that quantify what percentage of patients actually "fail" CS. "Failure" tends to be a subjective definition that varies among endoscopists. Our intent for the HCSR risk score is that it be applied to all patients and that it will be most useful in those patients when the endoscopist is unsure whether CS is appropriate. We also emphasize that although we envision the HCSR score as a tool applicable to all patients planned for GI endoscopy, our study population was restricted to patients who had been directed to CS. In other words, our dataset does not include patients directed to MAC, and the HCSR characteristics of those patients would be necessary to calculate the true prevalence of HCSRs in the overall outpatient GI endoscopy population at our institution. This makes establishment of positive or negative predictive values for the HCSR risk score a challenge. We see the prospective application and validation of our risk score in additional datasets as the next step for our work, and one that will be crucial before it can be used with high confidence at other institutions.

We have developed a score that predicts risk of HCSR during endoscopy based on 5 key patient and procedure characteristics: patient age, use of prescription opioids,

use of prescription benzodiazepines, and both EGD and colonoscopy within the same procedural window. The estimated AUC of 0.70 indicates that, although prediction accuracy can certainly be improved, most likely by the incorporation of variables that were not measured in our study, the HCSR risk score is relatively effective in predicting the risk of HCSRs. The fact that we observed similar predictive ability of the HCSR risk score in an independent validation series further supports its validity. Although the general increasing proportion of patients with HCSRs as the HCSR risk score increased that was observed in the original series was slightly less stable in the validation series, this is most likely due to the smaller number of patients with a high HCSR risk score in the latter series, which results in a lack of precision in estimated proportions in those patient groups. We suggest that patients with a low HCSR risk score proceed with CS assuming a low risk of adverse sedation-related outcomes, early procedure termination, and need for repeat endoscopy. Conversely, we recommend that preventive steps (such as preprocedural discontinuation of nonclonazepam benzodiazepines and opioids, especially in young patients) may be a reasonable option for patients with a risk score of 3.5 or higher. Alternatively, a score of 3.5 or higher could represent an acceptable indication for MAC instead of endoscopist-directed CS.

Our vision for the HCSR risk score is that it be used as an adjunct to the standard pre-endoscopy evaluation. Such a tool can easily be applied by physicians, advanced practice providers, and nurses because its components are simple to obtain and a score is quickly calculated without the need for complex equations. The interpretation of the score is the more challenging task that we leave to the endoscopist for whom we provide this article and the evidence and hope that its prospective application and further study will aid in refining it into a valid and useful tool. We propose the use of the HCSR risk score to mitigate these problems. Our study suggests that variables identified before GI endoscopy can be quantified in terms of their likelihood to portend a sedation failure in specific patients.

REFERENCES

1. iData Research. 75 million endoscopies performed annually according to iData Research procedure analysis. May 28, 2018. Available at: https://idataresearch.com/75-million-endoscopies-performed-annually-according-to-idata-research-procedure-analysis/ Accessed September 12, 2019.
2. Khiani VS, Soulos P, Gancayco J, et al. Anesthesiologist involvement in screening colonoscopy: temporal trends and cost implications in the Medicare population. Clin Gastroenterol Hepatol 2012;10:58-64.e1.
3. Early DS, Lightdale JR, Vargo JJ, et al. Guidelines for sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2018;87:327-37.
4. Predmore Z, Nie X, Main R, et al. Anesthesia service use during outpatient gastroenterology procedures continued to increase from 2010 to 2013 and potentially discretionary spending remained high. Am J Gastroenterol 2017;112:297-302.
5. Qadeer MA, Lopez AR, Dumot JA, et al. Hypoxemia during moderate sedation for gastrointestinal endoscopy: causes and associations. Digestion 2011;84:37-45.
6. Tobias JD, Leder M. Procedural sedation: a review of sedative agents, monitoring, and management of complications. Saudi J Anaesth 2011;5:395-410.
7. Coté GA, Hovis CE, Hovis RM, et al. A screening instrument for sleep apnea predicts airway maneuvers in patients undergoing advanced endoscopic procedures. Clin Gastroenterol Hepatol 2010;8:660-5.e1.
8. Gross JB, Bailey PL, Connis RT, et al. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.
9. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. World J Gastrointest Endosc 2013;5:527-33.
10. Adams MA, Prenovost KM, Dominitz JA, et al. Predictors of use of monitored anesthesia care for outpatient gastrointestinal endoscopy in a capitated payment system. Gastroenterology 2017;153:1496-503.e1.
11. Moons KM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (tripod): explanation and elaboration. Ann Intern Med 2015;162:W1-73.
12. Agrawal D, Rockey DC. Propofol for screening colonoscopy in low-risk patients: are we paying too much? JAMA Intern Med 2013;173:1836-8.
13. Inadomi JM. Editorial: Endoscopic sedation: Who, which, when? Am J Gastroenterol 2017;112:303-5.
14. Rex DK, Vargo JJ. Anesthetist-directed sedation for colonoscopy: a safe haven or siren's song? Gastroenterology 2016;150:801-3.
15. Sipe BW, Rex DK, Latinovich D, et al. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. Gastrointest Endosc 2002;55:815-25.
16. Cohen LB, DeLegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. Gastroenterology 2007;133:675-701.
17. Byrne MF, Chiba N, Singh H, et al. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. Can J Gastroenterol 2008;22:457-9.
18. Cohen LB, Benson AA. Issues in endoscopic sedation. Gastroenterol Hepatol 2009;5:565-70.
19. Singh H, Poluha W, Cheang M, et al. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev 2008;(4):CD006268.
20. Hassan C, Rex DK, Cooper GS, et al. Endoscopist-directed propofol administration versus anesthesiologist assistance for colorectal cancer screening: a cost-effectiveness analysis. Endoscopy 2012;44:456-64.
21. Zakeri N, Coda S, Webster S, et al. Risk factors for endoscopic sedation reversal events: a five-year retrospective study. Frontline Gastroenterol 2015;6:270-7.
22. Lebwohl B, Hassid B, Ludwin S, et al. Increased sedation requirements during endoscopy in patients with celiac disease. Dig Dis Sci 2012;57:994-9.
23. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64:1147.
24. Rex DK, Chen SC, Overhiser AJ. Colonoscopy technique in consecutive patients referred for prior incomplete colonoscopy. Clin Gastroenterol Hepatol 2007;5:879-83.
25. Vemulapalli KC, Rex DK. Water immersion simplifies cecal intubation in patients with redundant colons and previous incomplete colonoscopies. Gastrointest Endosc 2012;76:812-7.
26. Cadoni S, Falt P, Gallittu P, et al. Water exchange is the least painful colonoscope insertion technique and increases completion of unsedated colonoscopy. Clin Gastroenterol Hepatol 2015;13:1972-80.e3.
27. Papachristou GI, Gleeson FC, Papachristou DJ, et al. Endoscopist administered sedation during ERCP: impact of chronic narcotic/benzodiazepine use and predictive risk of reversal agent utilization. Am J Gastroenterol 2007;102:738.
28. Lee S-Y, Son HJ, Lee JM, et al. Identification of factors that influence conscious sedation in gastrointestinal endoscopy. J Korean Med Sci 2004;19:536-40.
29. DeLegge MH. The difficult-to-sedate patient in the endoscopy suite. Gastrointest Endosc Clin North Am 2008;18:679-93.

30. Peña LR, Mardini HE, Nickl NJ. Development of an instrument to assess and predict satisfaction and poor tolerance among patients undergoing endoscopic procedures. Dig Dis Sci 2005;50:1860-71.
31. Wong RC. The menu of endoscopic sedation: all-you-can-eat, combination set, á la carte, alternative cuisine, or go hungry. Gastrointest Endosc 2001;54:122-6.
32. Morgan J, Roufeil L, Kaushik S, et al. Influence of coping style and precolonoscopy information on pain and anxiety of colonoscopy. Gastrointest Endosc 1998;48:119-27.
33. Yacavone RF, Locke GR, Gostout CJ, et al. Factors influencing patient satisfaction with GI endoscopy. Gastrointest Endosc 2001;53:703-10.
34. Schutz SM, Lee JG, Schmitt CM, et al. Clues to patient dissatisfaction with conscious sedation for colonoscopy. Am J Gastroenterol 1994;89:1476-9.
35. Braunstein ED, Rosenberg R, Gress F, et al. Development and validation of a clinical prediction score (the SCOPE score) to predict sedation outcomes in patients undergoing endoscopic procedures. Aliment Pharmacol Ther 2014;40:72-82.

SUPPLEMENTARY TABLE 1. Specific types of benzodiazepines and opioids for cases (patients with high conscious sedation requirements) and controls (patients without high conscious sedation requirements)

Variable	Controls (n = 976), n (%)	Cases (n = 488), n (%)
Benzodiazepine type		
Alprazolam	63 (6.5)	58 (11.9)
Midazolam	0 (0.0)	0 (0.0)
Lorazepam	33 (3.4)	35 (7.2)
Clonazepam	35 (3.6)	18 (3.7)
Diazepam	8 (0.8)	10 (2.0)
Temazepam	6 (0.6)	10 (2.0)
Chlordiazepoxide	1 (0.1)	1 (0.2)
Oxazepam	0 (0.0)	0 (0.0)
Opioid type		
Hydrocodone	57 (5.8)	41 (8.4)
Oxycodone	32 (3.3)	32 (6.6)
Tramadol	32 (3.3)	27 (5.5)
Codeine	1 (0.1)	1 (0.2)
Morphine	1 (0.1)	2 (0.4)
Hydromorphone	7 (0.7)	3 (0.6)
Meperidine	0 (0.0)	1 (0.2)
Methadone (Dolophine, Methadose)	0 (0.0)	0 (0.0)
Other opioid	1 (0.1)	4 (0.8)

SUPPLEMENTARY TABLE 2. Patient and procedure characteristics for cases (patients with high conscious sedation requirements) and controls (patients without high conscious sedation requirements) for those patients aged ≤30 years

Variable	Controls (n = 36)	Cases (n = 77)
Age (years)	24.6 (17.2-29.3)	23.3 (16.3-29.9)
Race (non-white)	2 (5.6)	7 (9.1)
Sex (male)	11 (30.6)	29 (37.7)
Body mass index	25.4 (17.9-60.8)	23.6 (13.4-58.1)
≤25.00 kg/m^2	17 (48.6)	50 (65.8)
25.01-30.00 kg/m^2	10 (28.6)	6 (7.9)
30.01-35.00 kg/m^2	3 (8.6)	11 (14.5)
>35.00 kg/m^2	5 (14.3)	9 (11.8)
MELD score	6 (6, 6)	6 (6, 20)
≤6	36 (100)	74 (96.1)
7-14	0 (0.0)	2 (2.6)
≥15	0 (0.0)	1 (1.3)
History of sleep apnea	0 (0.0)	2 (2.6)
History of colon resection	2 (5.6)	3 (3.9)
History of small-bowel resection	0 (0.0)	5 (6.5)
Current alcohol use	14 (38.9)	36 (46.8)
Current tobacco use	2 (5.6)	12 (15.6)
Current medication use		
Benzodiazepines	5 (13.9)	14 (18.2)
Benzodiazepines (excluding clonazepam)	3 (8.3)	11 (14.3)
Opioids	2 (5.6)	15 (19.5)
Serotonin or norepinephrine reuptake inhibitors	8 (22.2)	15 (19.5)
Nonsteroidal anti-inflammatory drugs	4 (11.1)	10 (13.0)
Antiepileptic drugs	2 (5.6)	2 (2.6)
Tricyclic antidepressants	1 (2.8)	4 (5.2)
Antipsychotics	0 (0.0)	2 (2.6)
Restless leg syndrome medications	1 (2.8)	0 (0.0)
Magnesium	0 (0.0)	0 (0.0)
Iron sulfate	2 (5.6)	4 (5.2)
Proton pump inhibitors	7 (19.4)	28 (36.4)
Attention-deficit hyperactivity disorder medications	0 (0.0)	4 (5.2)
Diabetes medications	0 (0.0)	1 (1.3)
Procedure type		
EGD	20 (55.6)	30 (39.0)
Colonoscopy	5 (13.9)	10 (13.0)
Both EGD and colonoscopy	11 (30.6)	37 (48.1)
Procedure performed with a fellow	4 (11.1)	15 (19.5)

Values are number (%) except where indicated otherwise. The sample median (minimum, maximum) is given for continuous variables. Information was unavailable regarding body mass index for 1 control and 1 case.
MELD, Model for End-Stage Liver Disease.

SUPPLEMENTARY TABLE 3. Percentage of patients with high conscious sedation requirements according to the high conscious sedation requirement risk score

	Original series (488 cases, 976 controls)			Validation series (250 cases, 250 controls)				
	Percentage of patients with HCSRs			Percentage of patients with HCSRs				
HCSR risk score	Fraction (%) of patients with HCSRs in our case-control study	Assuming that the true percentage of cases is 1%	Assuming that the true percentage of cases is 5%	Assuming that the true percentage of cases is 10%	Fraction (%) of patients with HCSRs in our case-control study	Assuming that the true percentage of cases is 1%	Assuming that the true percentage of cases is 5%	Assuming that the true percentage of cases is 10%
0	18/128 (14.1)	0.3	1.7	3.5	19/74 (25.7)	0.3	1.8	3.7
0.5	48/264 (18.2)	0.4	2.3	4.7	37/91 (40.7)	0.7	3.5	7.1
1	61/264 (23.1)	0.6	3.1	6.3	32/83 (38.6)	0.6	3.2	6.5
1.5	104/324 (32.1)	0.9	4.7	9.5	53/97 (54.6)	1.2	6.0	11.8
2	89/233 (38.2)	1.2	6.1	12.1	49/70 (70.0)	2.3	10.9	20.6
2.5	54/92 (58.7)	2.8	13.0	24.0	25/35 (71.4)	2.5	11.6	21.7
3	63/90 (70.0)	4.5	19.7	34.1	14/27 (51.9)	1.1	5.4	10.7
3.5 to 5	51/69 (73.9)	5.4	23.0	38.6	21/23 (91.3)	9.6	35.6	53.8

The proportion of patients with HCSRs at each level of the HCSR risk score was estimated for the patients in our case-control study to assess the overall effectiveness of the score in discriminating between patients with and without HCSRs; however, these proportions are severely biased due to the 1:2 matched case-control study design (and the 1:1 matched design of the validation series). Therefore, we used Bayes' theorem to estimate what these proportions would be in the overall endoscopy patient population at our institution, assuming that the true proportion of patients with HCSRs is 1%, 5%, or 10%.
HCSR, High conscious sedation requirement.

SUPPLEMENTARY TABLE 4. Characteristics of the validation series of 250 cases (patients with high conscious sedation requirements) and 250 controls (patients without high conscious sedation requirements)

Variable	Controls (n = 250), n (%)	Cases (n = 250), n (%)
Midazolam >10 mg	0 (0.0)	48 (19.2)
Fentanyl >200 μg	0 (0.0)	21 (8.4)
Meperidine >100 mg	0 (0.0)	3 (1.2)
Incomplete procedure	0 (0.0)	0 (0.0)
Poor tolerance (nursing documentation)	0 (0.0)	75 (30.0)
Reversal agent needed	0 (0.0)	4 (1.6)
Aborted procedure	0 (0.0)	173 (69.2)
Age		
≤30.00 years	15 (6.0)	32 (12.8)
30.01-40.00 years	13 (5.2)	37 (14.8)
40.01-50.00 years	39 (15.6)	43 (17.2)
50.01-60.00 years	58 (23.2)	59 (23.6)
60.01-70.00 years	69 (27.6)	49 (19.6)
>70.00 years	56 (22.4)	30 (12.0)
Sex (female)	126 (50.4)	162 (64.8)
Benzodiazepines (excluding clonazepam)	16 (6.4)	34 (13.6)
Opioids	23 (9.2)	47 (18.8)
Procedure type		
EGD	87 (34.8)	84 (33.6)
Colonoscopy	138 (55.2)	100 (40.0)
Both EGD and colonoscopy	25 (10.0)	66 (26.4)