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Higher body mass index is strongly linked to poor outcomes in adult COVID-19 hospitalizations: A National Inpatient Sample Study

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Abstract

Aims: The coronavirus disease 2019 (COVID-19) pandemic has resulted in more than 6 million deaths worldwide. Studies on the impact of obesity on patients hospitalized with COVID-19 pneumonia have been conflicting, with some studies describing worse outcomes in patients with obesity, while other studies reporting no difference in outcomes. Previous studies on obesity and critical illness have described improved outcomes in patients with obesity, termed the "obesity paradox." The study assessed the impact of obesity on the outcomes of COVID-19 hospitalizations, using a nationally representative database.

Materials and Methods: ICD-10 code U071 was used to identify all hospitalizations with the principal diagnosis of COVID-19 infection in the National Inpatient Database 2020. ICD-10 codes were used to identify outcomes and comorbidities. Hospitalizations were grouped based on body mass index (BMI). Multivariable logistic regression was used to adjust for demographic characteristics and comorbidities.

Results: A total of 56,033 hospitalizations were identified. 48% were male, 49% were white and 22% were black. Patients hospitalized with COVID-19 pneumonia in the setting of obesity and clinically severe obesity were often younger. Adjusted for differences in comorbidities, there was a significant increase in mortality, incidence of mechanical ventilation, shock, and sepsis with increased BMI. The mortality was highest among hospitalizations with BMI ≥60, with an adjusted odds ratio of 2.66 (95% Confidence interval 2.18–3.24) compared to hospitalizations with normal BMI. There were increased odds of mechanical ventilation across all BMI groups above normal, with the odds of mechanical ventilation increasing with increasing BMI.

Conclusion: The results show that obesity is independently associated with worse patient outcomes in COVID-19 hospitalizations and is associated with higher inpatient mortality and higher rates of mechanical ventilation. The underlying

mechanism of this is unclear, and further studies are needed to investigate the cause of this.

KEYWORDS
acute hypoxic respiratory failure, ARDS, COVID-19, obesity

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in more than 1 million deaths in the United States to date, and more than 6 million deaths worldwide.[1,2] Although widespread vaccinations and advances in therapy options have improved outcomes in the recent months, COVID-19 still accounts for more than 2000 deaths weekly in the United States, and more than 3000 daily admissions.[1,3] Obesity and diabetes have been described as independent risk factors of poor outcomes in patients with COVID-19; however, the evidence behind this is not clear and epidemiological data is still lacking.[4] There have been mixed and conflicting reports regarding the association of obesity and poor outcomes in patients with COVID-19 infection.

Early studies of the association of body mass index (BMI) with COVID-19 reported increased prevalence of obesity in young patients with severe COVID-19 infection, with a study from 2020 showing that younger patients (<50 years of age) hospitalized with moderate-severe COVID-19 pneumonia had a higher mean BMI (43.1 vs. 30.1, $p = 0.02$) than older patients (>50 years of age), with and without diabetes and hypertension.[5] However, morbidity and mortality outcomes were not reported in this study. Early reports from Italy included a 331 patient cohort from the first 40 days of the pandemic in Italy and showed no significant differences in mortality between patients with a BMI over 30 kg/m^2 compared to those under 30 kg/m^2, controlling for other factors. However, patients with obesity were more likely to be admitted to the intensive care unit (ICU) than patients who did not have obesity.[6] Patients who were underweight were included in the <30 kg/m^2 group, however, limiting its interpretability. A large single center retrospective study in Bronx, NY, including 1274 hospitalized patients with COVID-19 pneumonia between 1 March and 30 June 2020, found no association between survival and BMI groups using a Kaplan–Meier survival estimate ($p = 0.7746$).[7] BMI class was not associated with difference in survival time in a multivariate analysis. However, patients who were overweight or obese had higher odds of requiring mechanical ventilation. It was notable that patients with obesity were also younger ($p < 0.001$). Lastly, a retrospective study of the first 277 consecutive COVID-19 patients admitted to Massachusetts General Hospital ICU found no difference in outcomes between BMI groups, including 30- and 60-day mortality and duration of mechanical ventilation.[8] However, this study did not control for comorbidities, and, similar to the studies by Bhasin et al.[5] and Zahid et al.,[7] patients with obesity tended to be younger (median age 56 [IQR 46–66] vs. 66 [IQR 54–76] $p < 0.05$) than patients without obesity.

On the other hand, reports from Mexico showed increased mortality in persons who were underweight or had obesity, with a retrospective cohort including 608 patients hospitalized from March to December of 2020 with COVID-19 pneumonia showing that mortality was highest in patients who were underweight (BMI <18.5 kg/m^2, 80% mortality), followed by patients who had obesity grade 3 (BMI >40 kg/m^2, 58.8% mortality) and then patients who had obesity grade 2 (BMI 35–39.9 kg/m^2, 50.0% mortality).[9]

The rising prevalence of obesity in the United States, and many other countries, increases the importance of research into the impact of obesity on mortality in both COVID-19 pneumonia and other viral diseases and increases the need for aggressive care and treatment of such patients. Given the conflicting nature of the previously published literature on the subject, the impact of obesity on patient outcomes with COVID-19 pneumonia was assessed using a large nationally representative database.

2 | MATERIALS AND METHODS

2.1 | Database

The National Inpatient Sample Database (NIS) is an all-payer inpatient database that is developed by the Healthcare Cost and Utilization Project. The database is constructed by the weighted and stratified sampling of all state inpatient databases. NIS 2020 contains 6,470,065 entries. Each entry represents a separate hospitalization. Repeated hospitalizations for the same patient might be captured as separate entries. The database provides valuable data on hospitalizations including demographics of the patient and admitting facility, principal and secondary diagnoses of the hospital stay, procedures performed during that hospital stay, and resource utilization data such as length of stay and total cost of stay. Data was extracted from discharge abstracts submitted by hospitals to data gathering agencies.

2.2 | Sampling

The database provides information on clinical diagnoses and procedures using the International Classification of Diseases – 10th revision – Clinical Modifications (ICD-10-CM). Clinical diagnoses are presented in 40 different variables, the first of which represents the principal diagnosis of the hospitalization. Similarly, procedures are presented in 25 different variables. ICD-10 code "U071" was used to

identify all hospitalizations with the principal diagnosis of COVID-19 infection. ICD-10 codes were also used to identify outcomes and comorbidities (Supporting Information S1). Patients younger than 18 years, elective admissions, absent BMI data, and BMI< 20 kg/m^2 were excluded. Remaining hospitalizations were grouped based on BMI. Figure 1 demonstrates the sampling process with the number of hospitalizations in each step.

2.3 | Outcomes

The primary outcome was in-hospital mortality rates of different BMI groups in hospitalizations with the principal diagnosis of COVID-19 infection. Secondary outcomes were the rates of mechanical ventilation, circulatory shock, venous thromboembolism events, and sepsis among the BMI groups. Anaphylactic shock was excluded from the definition of circulatory shock.

2.4 | Statistical analysis

Baseline characteristics are described and presented in Table 1. Analysis was done using IBM SPSS version 26. Sample weights were applied to all cases. Categorical variables were described as counts with percentages and compared using Pearson's Chi-square. Age was described using medians and compared using Kruskal-Wallis test, which accounts for the non-normality of distribution. For comparative analysis of the outcomes, a multivariable logistic regression model was constructed. All models were adjusted for age, gender, race, diabetes mellitus (DM), hypertension (HTN), dyslipidemia (DLD), solid malignancies, hematologic malignancies, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), end-stage renal disease, chronic liver disease, chronic left heart failure (CHF), tobacco abuse, and alcohol abuse. BMI group 20–24.9 kg/m^2 was considered a reference group for all comparisons. Adjusted odds ratios (OR) and 95% confidence intervals were reported for these models.

3 | RESULTS

3.1 | Baseline characteristics

A total of 56,033 hospitalizations were identified. 48% were male, 49% were White and 22% were Black. 2740 patients were of normal weight (BMI 20–24.9), 5281 patients were overweight (BMI 25–29.9), 13,681 patients had obesity class 1 (BMI 30–34.9), 12,397 patients had obesity class 2 (BMI 35–39.9), 10,646 had obesity class 3 (BMI 40–44.9), 5588 patients had a BMI of 45–49.9, 4468 had a BMI of 50–59.9, and 1709 patients had a BMI of ≥60. Significant differences were noted in the prevalence of DM, HTN, DLD, COPD, CAD, CHF, CKD, tobacco and alcohol abuse, as well as solid and hematologic malignancies across the BMI groups (Table 1).

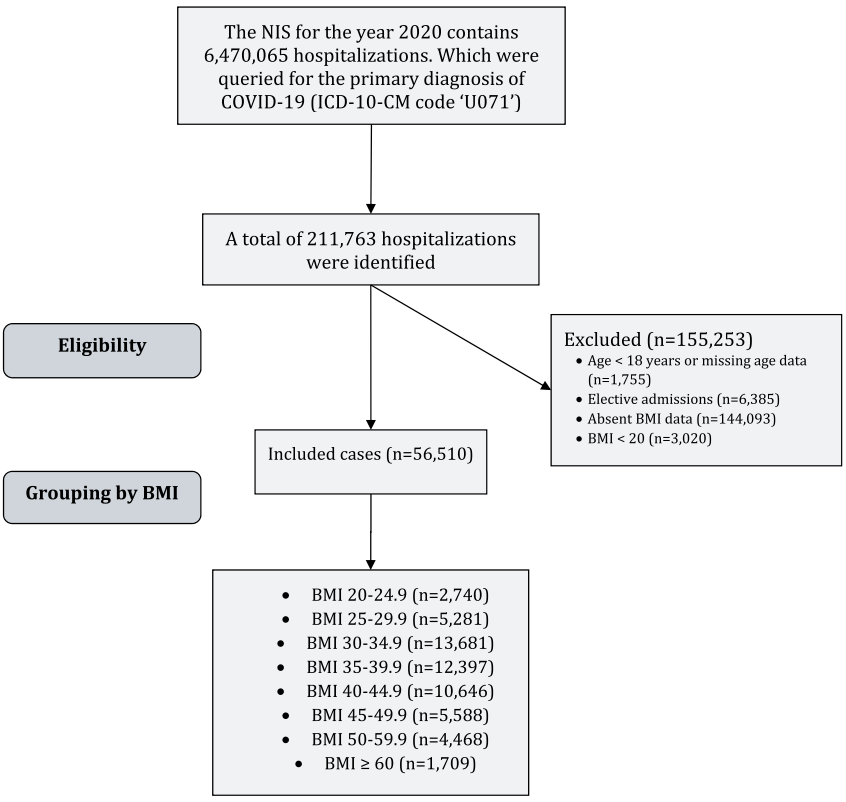

FIGURE 1 Patient selection and study design.

TABLE 1 Demographic and baseline characteristics of COVID-19 hospitalizations (*n*, %).

BMI Group	20–24.9	25–29.9	30–34.9	35–39.9	40–44.9	45–49.9	50–59.9	≥60	*p*-value
Total number	2740	5281	13,681	12,397	10,646	5588	4468	1709	
Age (years, median)	78	68	62	59	57	55	52	48	<0.001
Male sex	1451 (53)	3085 (58)	7610 (56)	6066 (49)	4445 (42)	2080 (37)	1521 (34)	563 (33)	<0.001
Race									
White	1491 (54)	2495 (47)	6606 (48)	5966 (48)	5288 (50)	2678 (48)	2089 (47)	727 (43)	<0.001
Black	463 (17)	850 (16)	2447 (18)	2538 (20)	2608 (24)	1490 (27)	1277 (29)	574 (34)	<0.001
Other	786 (29)	1936 (37)	4628 (34)	3893 (31)	2750 (26)	1420 (25)	1102 (25)	408 (24)	<0.001
Diabetes	928 (34)	2348 (44)	6404 (47)	5949 (48)	5472 (51)	2800 (50)	2244 (50)	838 (49)	<0.001
Hypertension	1964 (72)	3714 (70)	9307 (68)	8514 (69)	7550 (71)	3958 (71)	3148 (70)	1203 (70)	<0.001
Dyslipidemia	1245 (45)	2523 (48)	6381 (47)	5440 (44)	4324 (41)	2130 (38)	1522 (34)	511 (30)	<0.001
COPD	477 (17)	752 (14)	1703 (12)	1520 (12)	1477 (14)	849 (15)	645 (14)	280 (16)	<0.001
Coronary artery disease	35 (1)	96 (2)	187 (1)	125 (1)	100 (1)	40 (1)	22 (0)	6 (0)	<0.001
Chronic left heart failure	368 (13)	523 (10)	1290 (9)	1259 (10)	1365 (13)	776 (14)	631 (14)	295 (17)	<0.001
CKD/ESRD	732 (27)	1068 (20)	2358 (17)	2083 (17)	1917 (18)	994 (18)	711 (16)	251 (15)	<0.001
Chronic liver disease	43 (2)	86 (2)	218 (2)	188 (2)	151 (1)	81 (1)	63 (1)	24 (1)	0.936
Tobacco abuse	159 (6)	236 (4)	688 (5)	602 (5)	510 (5)	311 (6)	248 (6)	78 (5)	0.029
Alcohol abuse	63 (2)	118 (2)	225 (2)	169 (1)	138 (1)	56 (1)	36 (1)	9 (1)	<0.001
Solid malignancies	137 (5)	141 (3)	235 (2)	173 (1)	120 (1)	63 (1)	46 (1)	15 (1)	<0.001
Hematological malignancies	99 (4)	162 (3)	284 (2)	211 (2)	150 (1)	64 (1)	60 (1)	20 (1)	<0.001

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease.

3.2 | Outcomes

Unadjusted for comorbidities, the crude in-hospital mortality rate does not show a clear association with increased BMI, with the highest overall mortality seen in the normal BMI group (15.5%), followed by BMI group ≥60 (11.5%) followed by the overweight group (11.4%). Crude rate of mechanical ventilation was higher with increasing BMI. Adjusted for differences in age, gender, race, DM, HTN, DLD, CAD, COPD, CKD, chronic liver disease, CHF, tobacco abuse, alcohol abuse, solid malignancy and hematologic malignancy, there was a higher incidence of in-hospital mortality, incidence of mechanical ventilation, shock, and sepsis with increased BMI in the study population (Table 2).

The adjusted mortality was highest among hospitalizations with recorded BMI ≥60, with an adjusted odds ratio of 2.66 (95% Confidence interval [CI] 2.18–3.24) compared to hospitalizations with a normal BMI. There was also a significant increase in mortality seen in hospitalizations with BMI groups 50–59.9, 45–49.9, and 40–44.9, with odds ratio of 1.72, 1.51, and 1.35, respectively ($p < 0.05$). There was no significant difference in mortality seen with BMI groups 25–29.9, 30–34.9, and 35–39.9. There were also increased odds of mechanical ventilation across all BMI groups above normal, with the odds of mechanical ventilation increasing as BMI increases.

The odds of circulatory shock were higher in BMI groups 40–44.9, 50–59.9, and ≥60, with odds 1.40, 1.60, and 2.14, compared with the normal BMI group ($p < 0.05$). Odds of sepsis were also higher in BMI groups 40–44.9, 45–49.9, 50–59.9, and ≥60 compared to the normal BMI group ($p < 0.05$). However, there was no difference in the odds of venous thromboembolism between the groups.

4 | DISCUSSION

This large population-based study describes obesity rates in hospitalizations with a primary diagnosis of COVID-19, and seeks to identify the impact obesity has on patient outcomes. The results show that obesity was independently associated with worse outcomes, especially higher in-hospital mortality rates and higher rates of mechanical ventilation in COVID-19 pneumonia. Patients hospitalized with COVID-19 in the setting of obesity and clinically severe obesity were often younger, with the mean age of patients with a BMI ≥60 being 48, versus the mean age of patients with normal BMI being 78.

The study supports the finding of another population-based study involving more than 1.6 million patients hospitalized with COVID-19, which showed that obesity was a predictor of inpatient mortality, along with age, male sex, DM, CKD, CHF, arrhythmia and coagulopathy.[3] Similarly, a meta-analysis published in 2020 also showed that obesity increases the risk of hospitalizations, ICU

TABLE 2 Outcomes in Covid-19 hospitalizations grouped by BMI.

BMI (kg/m^2)	Count (%)	aOR	95% CI		*p*-value
Mortality					
20–24.9 (reference group)	424 (15.5)				
25–29.9	604 (11.4)	0.97	0.84	1.11	0.621
30–34.9	1219 (8.9)	0.96	0.84	1.09	0.496
35–39.9	1039 (8.4)	1.06	0.93	1.21	0.346
40–44.9	1016 (9.5)	1.35	1.18	1.54	<0.001
45–49.9	522 (9.3)	1.51	1.30	1.75	<0.001
50–59.9	409 (9.2)	1.72	1.46	2.02	<0.001
≥60	196 (11.5)	2.66	2.18	3.24	<0.001
Mechanical ventilation					
20–24.9 (reference group)	381 (13.9)				
25–29.9	860 (16.3)	1.31	1.14	1.49	<0.001
30–34.9	2139 (15.6)	1.38	1.23	1.56	<0.001
35–39.9	2027 (16.4)	1.57	1.39	1.78	<0.001
40–44.9	2022 (19.0)	1.98	1.74	2.24	<0.001
45–49.9	1131 (20.2)	2.26	1.98	2.58	<0.001
50–59.9	979 (21.9)	2.66	2.31	3.05	<0.001
≥60	448 (26.2)	3.55	3.01	4.18	<0.001
Circulatory shock					
20–24.9 (reference group)	67 (2.4)				
25–29.9	134 (2.5)	1.14	0.84	1.53	0.407
30–34.9	287 (2.1)	1.05	0.79	1.38	0.747
35–39.9	240 (1.9)	1.04	0.78	1.39	0.779
40–44.9	262 (2.5)	1.40	1.05	1.86	0.022
45–49.9	114 (2.0)	1.22	0.88	1.68	0.232
50–59.9	112 (2.5)	1.60	1.15	2.22	0.005
≥60	54 (3.2)	2.14	1.45	3.15	<0.001
Venous thromboembolism					
20–24.9 (reference group)	147 (5.4)				
25–29.9	256 (4.8)	0.97	0.79	1.20	0.777
30–34.9	599 (4.4)	0.92	0.76	1.12	0.411
35–39.9	514 (4.1)	0.92	0.76	1.12	0.413
40–44.9	445 (4.2)	0.98	0.80	1.20	0.817
45–49.9	257 (4.6)	1.12	0.90	1.40	0.303
50–59.9	205 (4.6)	1.15	0.91	1.46	0.228
≥60	80 (4.7)	1.23	0.92	1.66	0.166
Sepsis					
20–24.9 (reference group)	189 (6.9)				
25–29.9	400 (7.6)	1.16	0.97	1.40	0.101
30–34.9	898 (6.6)	1.10	0.93	1.30	0.281

(Continues)

TABLE 2 (Continued)

BMI (kg/m^2)	Count (%)	aOR	95% CI		p-value
35–39.9	724 (5.8)	1.03	0.87	1.23	0.698
40–44.9	790 (7.4)	1.42	1.19	1.68	<0.001
45–49.9	387 (6.9)	1.37	1.13	1.66	0.001
50–59.9	318 (7.1)	1.48	1.21	1.81	<0.001
≥60	113 (6.6)	1.42	1.10	1.83	0.007

Abbreviations: BMI, body mass index; CI, Confidence interval; OR, odds ratio.

admission, mechanical ventilation, and death in COVID-19 patients.[10] Similar results were identified in studies outside the US, including a study in Mexico involving 608 patients hospitalized with COVID-19 pneumonia, which showed increased mortality in patients who were underweight or obese. The results of this study are in contrast with studies from Italy,[6] New York, USA,[7] and Massachusetts, USA,[8] all of which found no significant difference in mortality based on BMI group. These studies may have been limited, however, by inclusion of patients who were underweight in the non-obese group[6] and the difference of comorbidities was not accounted for.[8]

The results are also in contrast to some of the studies from the pre-COVID era about the impact of obesity in critical illness, with multiple studies describing a protective effect for higher BMI in critical illness, including a large meta-analysis of five trials with 6268 patients, which showed that obesity may be protective in patients admitted with Acute Respiratory Distress Syndrome (ARDS), with an OR of 0.68 (95% CI [0.57–0.80], $p < 0.00001$), while being underweight was associated with higher mortality with an OR of 1.59 (95% CI [1.22–2.08], $p = 0.0006$), compared to normal weight.[11] Another metanalysis showed a similar mortality benefit for obesity in patients admitted to the ICU with sepsis, severe sepsis, or septic shock.[12] This observed effect has been termed the "obesity paradox." Theories to explain this include that obesity, and excess adipose tissue, is associated with increased renin-aldosterone system activity and hypertension, which can potentially provide hemodynamic protection in the setting of sepsis, with decreased fluid administration by clinicians and less need of the use of vasopressors.[13] Additionally, there is some evidence that increased lipoproteins and adipose tissue can bind bacterial toxins and inactivate lipopolysaccharides.[14,15] It has also been suggested that obesity provides an abundance of energy reserve that helps in the catabolic state of sepsis and critical illness.[16] Specifically in the setting of ARDS, there is a suggestion that the chronically activated immune system in obesity can provide some protection against the cytokine storm that underlies the pathophysiology of ARDS.[17]

It is unclear why this "obesity paradox" does not apply for COVID-19 pneumonia patients. It has been suggested that critically ill patients with obesity may do better outside the COVID-19 pandemic due to a lower threshold to initiate aggressive care and escalate the level of care, with earlier admission to the ICU,[17] which is a privilege that was not available in the setting of a global pandemic and a strained healthcare system.[18] Other explanations that have been proposed include possible misclassification of patients with obesity as "ARDS" in the pre-COVID-19 studies, where hypoxia and chest infiltrates may be due to a less severe underlying condition such as heart failure, obesity hypoventilation syndrome, and atelectasis. There may also be a difference in the modulation of key immune cells in obesity in the setting of viral infections. A study in 2012 showed that patients with clinically severe obesity had increased peripheral blood CD4+ T cells with increased proportion of T regulatory and Th2 subtypes, which are anti-inflammatory cells, and can potentially result in higher viral loads during infections.[19,20] Adipocytokines (proinflammatory and anti-inflammatory factors released by adipose tissues) have been suggested as a potential explanation for the difference in outcomes. However, a recently published study in July of 2022 looked at the serial plasma levels of leptin, adiponectin, resistin, along with other inflammatory cytokines, and showed although there was higher leptin and lower adiponectin levels in patients who were overweight or obese ($p < 0.001$), there was no difference in the levels between survivors and non survivors, nor ICU and non-ICU patients. Resistin levels were higher in non survivors and ICU patients ($p < 0.001$), but there was no difference in resistin levels between patients with normal weight and patients who were overweight or obese ($p = 0.12$).[21]

4.1 | Limitations

This study has several limitations, which are important to note. First, the NIS is an administrative claim-based database that uses ICD-10-CM codes for the identification of disease processes, which introduces the possibility of misclassification bias. However, only patients with a principal diagnosis of COVID-19 infection were included in this study, which may minimize this bias. In addition, outcomes of death and intubation have clear definitions and thus less likely to be misclassified. The study does not take into account the different strains of COVID-19 virus, which may affect different populations differently, as well as the changing treatments that were offered in the early phase as compared to the later phases. There is also no information about vaccination status, which can be a confounder as patients who were older, had obesity, or with other co-morbidities were prioritized for vaccination early in the pandemic. The large sample size of the NIS database increases the power of the study and helps compensate for some of these limitations.

5 | CONCLUSION

This study shows that increasing BMI is independently associated with poor outcomes in hospitalizations with COVID-19 infections. Further studies are needed to identify the underlying mechanism for this.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ali Abdelhay. The first draft of the manuscript was written by Ahmed Elkhapery and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any competing interests. The authors do not have financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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