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Restrictive vs Liberal Physical Restraint Strategies in Critically Ill Patients
The R2D2-ICU Randomized Clinical Trial

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IMPORTANCE The effect of wrist-strap physical restraints on outcomes in patients receiving mechanical ventilation in the intensive care unit (ICU) remains uncertain.

OBJECTIVE To investigate the effect of a low-use wrist-strap physical restraint strategy in critically ill patients receiving invasive mechanical ventilation.

DESIGN, SETTING, AND PARTICIPANTS Open-label randomized clinical trial conducted across 10 ICUs in France. Between January 5, 2021, and January 2, 2024, 405 adult patients who had initiated invasive mechanical ventilation within the previous 6 hours and were expected to require ventilation for at least 48 hours were enrolled. Follow-up was completed on May 17, 2024. Statistical analysis was conducted from June 1, 2025, to December 15, 2025.

INTERVENTIONS Patients were randomized to undergo either a restrictive, low-use physical restraint strategy (wrist straps avoided unless necessary because of severe agitation, defined as a Richmond Agitation-Sedation Scale score of ≥3 [on a scale from −5 (unresponsive) to 4 (combative)]; n = 201) or a liberal, high-use strategy (wrist straps applied systematically and reassessed daily; n = 204). Discontinuation of restraints was allowed in patients who were awake or extubated without delirium (measured via the Confusion Assessment Method for the ICU).

MAIN OUTCOMES AND MEASURES The primary outcome was the number of days alive without coma or delirium during the first 14 days after randomization. Secondary outcomes included incidence of self-extubation and day-90 mortality.

RESULTS Among 396 patients with available primary outcome data, the median (IQR) age was 65 (56-73) years, 245 (62%) were male, and the median (IQR) Sequential Organ Failure Assessment score was 7 (4-10). The mean days alive without coma or delirium were 6.67 days (95% CI, 5.69-7.65) in the low-use strategy group and 6.30 days (95% CI, 5.35-7.24) in the high-use strategy group (adjusted mean difference, 0.37 days [95% CI, −0.71 to 1.46]; $P = .51$). Self-extubation occurred in 18 patients (9.2%) in the low-use strategy group and 17 (8.5%) in the high-use strategy group, and day-90 mortality was 37.2% and 41.0%, respectively.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, among adult patients receiving mechanical ventilation in the ICU, a low-use wrist-strap physical restraint strategy compared with a high-use strategy did not reduce days free of delirium or coma at 14 days.

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Group Information: The members of the R2D2-ICU Investigator Study Group appear in Supplement 2.

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Physical restraint, most often in the form of wrist straps, is widely used in the intensive care unit (ICU) to prevent self-injury and inadvertent device removal.[1] Despite marked variation in practice worldwide, studies suggest that approximately one-half of patients are restrained during ICU stay.[2-5] In many ICUs, prophylactic physical restraint is applied in a systematic manner among patients receiving mechanical ventilation, especially in larger ICUs with lower nurse to patient ratios.[4,6] Other units have adopted a more restrictive, low-use approach to physical restraint, in which restraints are not applied routinely but are permitted only when predefined clinical criteria are met, typically severe agitation posing an immediate safety risk.

Despite its widespread use, the benefits of physical restraint in the ICU have not been demonstrated.[1] In high-acuity settings, where patients may be delirious or agitated and staffing resources are limited, restraint is often regarded as a pragmatic safety measure. It may help prevent complications of agitation, which has been associated with unplanned extubation, infections, and prolonged ICU stay.[7] Concerns have also been raised regarding potential harms associated with physical restraint.[8] Restraints can increase stress, discomfort, and agitation, which in turn may prompt escalation of sedative and analgesic exposure. Together, these effects may increase the risk of coma or delirium,[9] which are linked to greater mortality,[10] long-term cognitive decline,[11] and posttraumatic stress disorder.[12] However, whether lower use of physical restraints can reduce coma or delirium and improve clinical outcomes remains uncertain. The Restrictive Use of Restraints and Delirium Duration in ICU (R2D2-ICU) trial was conducted to address this issue.[13]

Key Points

Question Does a restrictive (low-use) wrist-strap physical restraint strategy, compared with a liberal (high-use) strategy, reduce coma or delirium in adult patients receiving mechanical ventilation in the intensive care unit?

Findings In this randomized clinical trial of 405 adults receiving invasive mechanical ventilation, the number of days alive without coma or delirium during the first 14 days after randomization did not differ between the low- and high-use restraint strategies (6.67 vs 6.30 days). Delirium; self-extubation; day-90 mortality; and 90-day functional, cognitive, and psychological outcomes were similar between groups.

Meaning In adult patients receiving mechanical ventilation in the intensive care unit, a low-use wrist-strap physical restraint strategy did not improve coma- or delirium-free days.

Methods

Trial Design and Oversight

R2D2-ICU was an institutionally sponsored, unblinded, multicenter, open-label, parallel-group, superiority randomized clinical trial, with centralized randomization conducted in 10 ICUs in France, from January 2021 through January 2024. The protocol (previously published[13]) was approved by the Comité de Protection des Personnes Île-de-France III (CPP19.09.06.37521), and written informed consent was obtained from all patients or their legally authorized representatives. The trial was registered on ClinicalTrials.gov before enrollment and followed the CONSORT 2025 updated guideline for reporting randomized clinical trials.[14] Patients and the public were not involved in the design, conduct, or reporting of the trial.

Patients

We included adults who were consecutively admitted to the ICU, had received invasive mechanical ventilation for less than 6 hours at the time of screening, and for whom ongoing mechanical ventilation was anticipated to continue for at least 48 hours. Eligible patients had to be candidates for physical restraint, defined as not being under restraint at the time of screening and without a preexisting written medical prescription for restraint. The main exclusion criteria were documented delirium prior to ICU admission, assessed with the Confusion Assessment Method for the ICU (CAM-ICU), a validated tool that evaluates acute onset or fluctuating mental status, inattention, altered consciousness, and disorganized thinking (CAM-ICU results are recorded as positive [delirium present] or negative [delirium absent])[15]; a known diagnosis of dementia defined by a score of less than 24 on the Mini-Mental State Examination (scores range from 0 to 30, with lower scores indicating poorer cognitive performance)[16]; anticipated alcohol withdrawal syndrome; admission for primary neurological disorder; and preexisting visual or auditory impairment. Additional details regarding inclusion and exclusion criteria are available in eTable 1 in Supplement 1. Organ dysfunction was assessed using the Sequential Organ Failure Assessment score, which ranges from 0 to 24, with higher scores indicating greater severity of organ dysfunction.[17]

Trial Procedures

Eligible patients were randomly assigned in a 1:1 ratio to undergo either a restrictive, low-use strategy to physical restraint or a liberal, high-use strategy. Randomization was conducted centrally using a computer-generated sequence with randomly varying block sizes and stratified according to trial site, age (<65 or ≥65 years), and presence of coma at initiation of invasive mechanical ventilation, defined by a score on the Richmond Agitation-Sedation Scale (RASS) of -4 or -5. The RASS measures levels of consciousness on a scale from −5 (unresponsive) to 4 (combative).[18]

Physical restraint consisted exclusively of 2-point wrist straps. The assigned strategy—either low or high use—was maintained until the earliest occurrence of one of the following: day 14 in the ICU, readiness for ICU discharge (defined as the absence of need for vital organ support and discontinuation of central and/or arterial catheterization), or death.

In the low-use strategy group, wrist-strap restraints were permitted only in case of severe agitation, defined as a RASS score of 3 or higher (very agitated or combative) on any given day between days 0 and 14.

In the high-use strategy group, wrist-strap restraints were applied systematically from day 0 and reassessed daily. Discontinuation of physical restraint was permitted under the following conditions: (1) the patient was awake and not delirious (defined as a RASS score greater than −4 and a negative CAM-ICU) or (2) the patient was extubated and not delirious (defined as no longer receiving invasive mechanical ventilation and a negative CAM-ICU). Physical restraints could be reinstated in cases of recurrent severe agitation, regardless of ventilation status.

All patients received standardized management of analgesia, sedation, delirium, weaning from mechanical ventilation, and mobilization in accordance with guidelines (eTable 2 in Supplement 1 and the Study Protocol in Supplement 3).[1] Trained nursing staff assessed pain every 4 hours using the Behavioral Pain Scale (scores range from 3 to 12, with higher scores indicating more severe pain),[19] level of consciousness with the RASS every 4 hours, and delirium with the CAM-ICU every 12 hours. Staffing intensity was consistent with national standards, with a nurse to patient ratio ranging from 1:2.5 to 1:3 across centers (eTable 2 in Supplement 1). A day of coma was defined as any day on which the RASS score was −4 or −5 at any time and a day of delirium as any day with at least 1 positive CAM-ICU assessment.

Outcomes

Outcomes were collected by trained study coordinators who were not involved in routine ICU care. The primary outcome was the number of days alive without delirium or coma during the first 14 days following randomization. Secondary outcomes assessed over the same 14-day period included the incidence and duration of delirium and agitation; duration and cumulative dose of exposure to analgesics (sufentanil), propofol, benzodiazepines, antipsychotic agents (haloperidol, levomepromazine, and cyamemazine), and dexmedetomidine; patient mobility measured by a mobilization scale (ranging from 0 [no mobilization] to 4 [ambulating])[20]; incidence of self-extubation; incidence of unplanned device removal, defined as withdrawal of invasive vascular (central venous, arterial, or dialysis catheters), urinary, or drainage devices; and incidence of new pressure ulcers, defined as stage III or IV ulcers according to the National Pressure Injury Advisory Panel.[21] Other outcomes included ventilator-free days; length of stay in the ICU and hospital; and ICU and day-90 mortality. At 90 days after randomization, cognitive function was assessed using both the Mini-Mental State Examination[16] and the Frontal Assessment Battery (scores range from 0 to 18, with higher scores indicating better performance).[22] Functional outcome was evaluated using the Functional Independence Measure (scores range from 18 to 126, with higher scores indicating greater independence),[23] and posttraumatic stress symptoms were assessed with the Impact of Event Scale–Revised version (a 22-item questionnaire yielding a total score from 0 to 88, with higher scores indicating greater symptom severity)[24] through either an in-person or videoconference interview.

Statistical Analysis

Statistical analysis was conducted from June 1, 2025, to December 15, 2025. We estimated that a sample size of 422 patients would provide 90% power to detect a 1-day increase in delirium- and coma-free days in the low-use physical restraint group, assuming an SD of 3 days and a 2-sided α level of .05.[7,9]

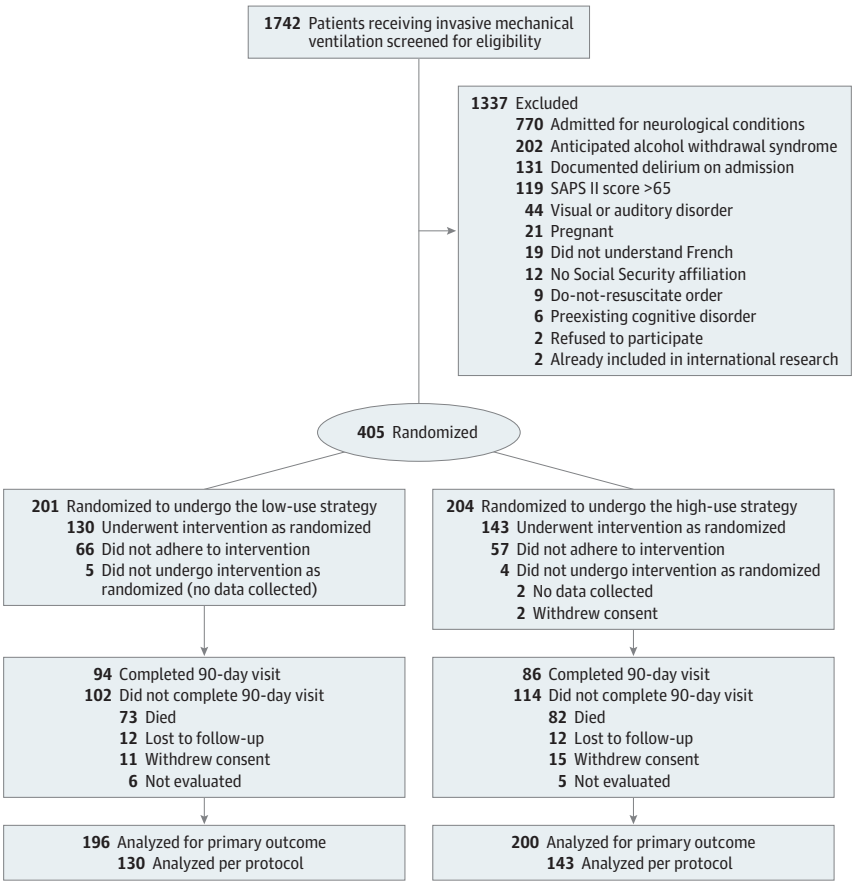
Baseline characteristics are reported as means with SDs or medians with IQRs, as appropriate. All analyses are reported with 95% CIs. No adjustments were made for multiple comparisons.[25]

The primary analysis population included all patients who underwent randomization and provided consent for use of their data. Analyses were performed according to the prepublished statistical analysis plan.[13] Models were adjusted for stratification variables (age and coma status at admission; trial site excluded). For the primary outcome, we used a linear regression model to estimate the adjusted mean difference between groups. Adjusted mean differences were obtained from the *emmeans* R package, which computes means adjusted for covariates from the fitted model. Because of the nonnormal distribution, 95% CIs were derived from 5000 bootstrap resamples. Missing data for the primary outcome were handled using a deterministic rule-based approach, according to prespecified rules based on the availability of RASS and CAM-ICU assessments during the 14-day trial period. Last observation carried forward was applied only when the final scheduled assessment was missing. Ventilator-free days were derived using a deterministic classification based on daily mechanical ventilation status and survival. When necessary, missing information was completed using adjacent clinical records. No imputation method for missing data was performed for the other secondary end points.

The primary outcome was also analyzed in the per-protocol population, defined as patients whose intervention was managed in adherence with the physical restraint rules of their assigned strategy. Prespecified subgroup analyses were performed according to trial site, age (<65 vs ≥65 years), coma status at randomization, and COVID-19 status at admission. Post hoc subgroup analyses according to admission type (medical vs surgical), sex, and severity of illness (Simplified Acute Physiology Score II <45 vs ≥45) were added. Nonadherence was defined as the absence of the assigned intervention for 4 or more consecutive hours during the protocol-defined treatment period. Due to the rate of nonadherence in both groups, a post hoc per-protocol analysis was performed using inverse probability weighting (g methods[26]) to account for measured predictors of nonadherence (including age, hypertension, Simplified Acute Physiology Score II, admission type, coma, physical restraint prescription, antipsychotic use, and midazolam use). Another post hoc subgroup analysis was performed, excluding patients who remained comatose throughout the ICU stay up to day 14.

Secondary continuous outcomes were analyzed with linear regression and secondary binary outcomes at 90 days with logistic regression. A 2-sided $P < .05$ was considered significant for the primary outcome. Analyses were performed with R version 4.1.2 (R Foundation).

Figure 1. Flow Diagram of Patient Recruitment, Randomization, and Outcomes in the Restrictive Use of Restraints and Delirium Duration in the Intensive Care Unit (R2D2-ICU) Trial



SAPS II indicates Simplified Acute Physiology Score II.

Results

Patients

Between January 5, 2021, and January 2, 2024, a total of 1742 patients were eligible for inclusion and 405 underwent randomization; 201 were randomized to the low-use strategy group and 204 to the high-use strategy group (**Figure 1**). A total of 9 patients (5 in the low-use strategy group and 4 in the high-use strategy group) were excluded after randomization, with 396 patients for the primary analysis. Age (median [IQR], 65 [55-72] vs 66 [56-73] years), medical admission rate (188 [95.9%] vs 182 [91.0%]), Sequential Organ Failure Assessment score (median [IQR], 7 [4-10] vs 7 [4-9]), ongoing propofol use (150 of 192 [78.1%] vs 146 of 196 [74.5%]), and sufentanil use (172 of 192 [89.6%] vs 165 of 196 [84.1%]) were similar between the low- and high-use groups, respectively (**Table 1**).

Intervention and Adherence to Protocol

Details about exposure to physical restraints are provided in eFigure 1 in Supplement 1.

Among patients randomized to the low-use group, wrist-strap restraints were applied on any given day in 71 of 196 patients (36.2%), and the median (IQR) daily time spent with physical restraints was 0 (0-1.4) hours (eTable 4 in Supplement 1). Wrist-strap restraints were applied in accordance with predefined criteria (eg, in case of severe agitation) in 5 of 196 patients (2.6%), and 66 of 196 patients (33.7%) underwent exposure to physical restraint for greater than 4 hours on any given day in the absence of severe agitation (eTable 3 in Supplement 1). In the 66 patients who were nonadherent, the median (IQR) daily time spent with physical restraints was 3.8 (8-24) hours (eTable 5 in Supplement 1).

Among patients randomized to the high-use group, wrist-strap restraints were applied on any given day in 200 patients (100%) and the median (IQR) daily time spent with physical restraints was 16.8 (10.3-23.6) hours (eTable 4 in Supplement 1). Wrist straps were removed on any given day in the absence of predefined criteria (eg, awake or extubated without delirium) in 57 of 200 patients (28.5%). In the 57 patients who were nonadherent, the median (IQR) daily time spent in physical restraints was 13.7 (6.1-18.2) hours (eTable 6 in Supplement 1).

Primary Outcome

Delirium assessment was attempted at 78.9% of all available assessment points (2462 of 3120 protocolized twice-daily CAM-ICU assessments). The median (IQR) number of assess-

Table 1. Characteristics of Patients at Baseline

Characteristic	Strategy, No. (%)	
	Low use (n = 196)	High use (n = 200)
Demographics		
Age, y		
Median (IQR)	65 (55 to 72)	66 (56 to 73)
≥65	95 (48.5)	101 (50.5)
≥80	16 (8.2)	9 (4.6)
Sex		
Female	68 (35)	83 (41.5)
Male	128 (65.3)	117 (58.5)
BMI, median (IQR)[a]	27 (24 to 31)	26 (23 to 30)
Medical history		
Hypertension	69 (35.2)	75 (37.5)
Chronic kidney disease, No./total No. (%)	21/195 (10.7)	21/200 (10.5)
Alcohol use disorder, No./total No. (%)	19/194 (9.8)	22/199 (11.0)
Congestive heart failure	19 (9.7)	17 (8.5)
Neurologic disorder[b]	19 (9.7)	17 (8.5)
Chronic liver disease	10 (5.1)	13 (6.5)
Type of ICU admission		
Medical	188 (95.9)	182 (91.0)
Emergency surgery	5 (2.6)	15 (7.5)
Elective surgery	3 (1.5)	3 (1.5)
Patient location before ICU admission		
Prehospital/emergency department	119 (60.7)	129 (64.5)
Hospital wards	66 (33.7)	64 (32.0)
Other ICU/operating room	11 (5.6)	7 (3.5)
Reason for ICU admission		
Respiratory	136 (69.4)	135 (67.5)
Cardiovascular	22 (11.2)	37 (18.5)
Neurological	16 (8.2)	11 (5.5)
Kidney	5 (2.6)	5 (2.5)
Abdominal	14 (7.1)	9 (4.5)
Surveillance	0	2 (1.0)
ICU room with natural light exposure, No./total No. (%)	154/193 (79.8)	156/191 (81.7)
COVID-19 infection at ICU admission	38 (19.4)	36 (18.0)
Septic shock at ICU admission	77 (39.3)	87 (43.5)
Reason for intubation		
Acute respiratory failure	141 (71.9)	140 (70.0)
Shock	29 (14.8)	29 (14.5)
Altered mental status	19 (9.7)	17 (8.5)
Other[c]	7 (3.6)	12 (6.0)
Time from ICU admission, median (IQR), h[d]		
To randomization	8 (3 to 26)	7 (3 to 24)
To intubation	4 (1 to 24)	3 (0 to 21)
Severity scores at randomization, median (IQR)		
SAPS II[e]	42 (31 to 53)	43 (31 to 54)
SOFA[f]	7 (4 to 10)	7 (4 to 9)
Clinical status at randomization		
RASS score, median (IQR)[g]	−5 (−5 to −4)	−5 (−5 to −4)
Comatose (RASS −4 or −5)	173 (88.2)	174 (87.0)

(continued)

Table 1. Characteristics of Patients at Baseline (continued)

Characteristic	Strategy, No. (%)	
	Low use (n = 196)	High use (n = 200)
Ventilation mode		
Assist-control ventilation, No./total No. (%)	190/192 (98.9)	196/199 (98.5)
Pressure support, No./total No. (%)	2/192 (1.0)	3/199 (1.5)
PEEP, median (IQR)[h]	8 (5 to 10)	8 (5 to 10)
FIo_2, median (IQR)[i]	70 (50 to 100)	60 (40 to 100)
Catecholamine infusion, No./total No. (%)	119/194 (61.3)	132/199 (66.3)
Sedation, No./total No. (%)		
Propofol	150/192 (78.1)	146/196 (74.5)
Midazolam	56/192 (29.2)	62/196 (31.6)
Dexmedetomidine	0/192	2/196 (1.0)
Analgesia, No./total No. (%)		
Sufentanil	172/192 (89.6)	165/196 (84.1)
Fentanyl	1/192 (0.5)	3/196 (1.5)
ECMO, No./total No. (%)	14/195 (7.2)	19/200 (9.5)
Kidney replacement therapy, No./total No. (%)	10/195 (5.1)	6/200 (3.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECMO, extracorporeal membrane oxygenation; FIo_2, fraction of inspired oxygen; ICU, intensive care unit; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation-Sedation Scale; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

[a] Median BMI was determined for 185 patients in the low-use strategy group and 191 patients in the high-use strategy group.

[b] Stroke, epilepsy, or cognitive impairment.

[c] Postoperative or multiple trauma.

[d] Median time from ICU admission to randomization and to intubation were both determined for 195 patients in the low-use group and 200 patients in the high-use group.

[e] Scores range from 0 to 163, with higher scores indicating greater severity of illness.

[f] Scores range from 0 to 24, with higher scores indicating greater organ dysfunction.

[g] Scores range from −5 (unarousable) to 4 (combative), with 0 indicating an alert and calm state.

[h] Pressure maintained in the lungs at the end of expiration during mechanical ventilation. Median PEEP was determined for 191 patients in the low-use group and 196 patients in the high-use group.

[i] Median FIo_2 was determined for 192 patients in the low-use group and 193 patients in the high-use group.

ments per patient was 5 (0-10) in the low-use group and 4 (0-8) in the high-use group. In the primary analysis population, 56 patients (14.1%) had at least 1 missing assessment. The mean number of days alive without delirium or coma at 14 days was 6.67 days (95% CI, 5.69-7.65) in the low-use group and 6.30 days (95% CI, 5.35-7.24) in the high-use group (adjusted mean difference, 0.37 days [95% CI, −0.71 to 1.46]; P = .51) (**Table 2**). Clinical status during the 14-day intervention period is presented in **Figure 2**. Over the 14-day study period, the median (IQR) percentage of assessments with a RASS score greater than −4 was 56.5% (52.0%-57.8%) in the low-use group and 59.0% (54.1%-62.8%) in the high-use group (eFigure 2 in Supplement 1).

Secondary Outcomes

The mean number of days alive without coma at 14 days was 5.12 days (95% CI, 4.36-5.88) in the low-use group and 4.99 days (95% CI, 4.26-5.73) in the high-use group (adjusted mean difference, 0.004 days [95% CI, −0.70 to 0.98]). Delirium occurred in 122 patients (62.2%) in the low-use group and 135 (67.5%) in the high-use group (adjusted risk ratio, 0.92 [95% CI, 0.80-1.07]). The adjusted mean difference of number of days alive with agitation at 14 days was 0.03 (95% CI, −0.08 to 0.14). There were no significant differences in cumulative doses of sufentanil, propofol, midazolam, antipsychotics (haloperidol, levomepromazine, and cyamemazine), or dexmedetomidine (eFigures 3-7 in Supplement 1) at 14 days. The mean ventilator-free days at day 14 were 5.28 (95% CI, 4.38-6.19) in the low-use group and 5.09 (95% CI, 4.22-5.97) in the high-use group (adjusted mean difference, 0.19 days [95% CI, −0.81 to 1.18]). The mean mobilization score was greater in the low-use group (0.49 [95% CI, 0.41-0.59] vs 0.41 [95% CI, 0.32-0.50]; adjusted mean difference, 0.09 [95% CI, −0.01 to 0.19]), although the proportion of patients with a score of greater than 2 at day 14 was similar (17 [8.7%] vs 17 [8.5%]) (eFigure 8 in Supplement 1).

Self-extubation occurred in 18 patients (9.2%) in the low-use group and 17 (8.5%) in the high-use group. Unplanned device removal occurred in 2 patients (1.0%) and 1 patient (0.5%), respectively. Pressure ulcers were reported in 30 patients (15.3%) and 34 patients (17.0%), respectively. The cumulative incidence of death up to 90 days did not differ significantly between groups (**Figure 3**A). Among survivors, outcomes assessed at 90 days were not significantly different in functional outcomes, cognitive function, or posttraumatic stress symptoms (Table 2) (eTable 7 in Supplement 1).

Subgroup and Sensitivity Analyses

There were no significant differences in the primary analysis among subgroups defined by age, sex, presence of coma at ran-

Table 2. Primary and Secondary Patient Outcomes

Outcome	Strategy, mean (95% CI)		Adjusted (95% CI)	
	Low use (n = 196)	High use (n = 200)	Mean difference	Risk ratio or hazard ratio[a]
Primary outcomes				
Days alive without delirium or coma at 14 d	6.67 (5.69 to 7.65)	6.30 (5.35 to 7.24)	0.37 (−0.71 to 1.46)	NA
Days alive without coma at 14 d	5.12 (4.36 to 5.88)	4.99 (4.26 to 5.73)	0.004 (−0.70 to 0.98)	NA
Days alive without delirium at 14 d	3.10 (2.49 to 3.72)	2.64 (2.05 to 3.23)	0.46 (−0.23 to 1.17)	NA
Secondary outcomes				
Delirium incidence at 14 d, No. (%)	122 (62.2)	135 (67.5)	NA	0.92 (0.80 to 1.07)
Days alive with agitation at 14 d	0.17 (0.07 to 0.27)	0.14 (0.05 to 0.24)	0.03 (−0.08 to 0.14)	NA
Cumulative dose of sufentanil at 14 d, mg	0.09 (0.07 to 0.12)	0.10 (0.08 to 0.12)	0 (−0.03 to 0.02)	NA
Cumulative dose of propofol at 14 d, mg	1392 (1100 to 1684)	1251 (969 to 1533)	141 (−194 to 451)	NA
Cumulative dose of midazolam at 14 d, mg	35.50 (20.92 to 50.08)	30.18 (16.10 to 44.27)	5.32 (−10.74 to 22.00)	NA
Cumulative dose of antipsychotics at 14 d, mg[b]	1.72 (0 to 3.80)	2.25 (0.24 to 4.26)	−0.54 (−2.88 to 1.65)	NA
Cumulative dose of dexmedetomidine at 14 d, µg/kg	0.44 (0.03 to 0.84)	0.71 (0.32 to 1.10)	−0.27 (−0.73 to 0.16)	NA
Ventilator-free days at 14 d	5.28 (4.38 to 6.19)	5.09 (4.22 to 5.97)	0.19 (−0.81 to 1.18)	NA
Mobilization score[c]				
Score	0.49 (0.41 to 0.59)	0.41 (0.32 to 0.50)	0.09 (−0.01 to 0.19)	NA
Score >2 at 14 d, No. (%)	17 (8.7)	17 (8.5)	NA	1.01 (0.53 to 1.91)
Self-extubation and device removal at 14 d, No. (%)				
Self-extubation	18 (9.2)	17 (8.5)	NA	1.11 (0.59 to 2.07)
Unplanned device removal[d]	2 (1.0)	1 (0.5)	NA	2.17 (0.21 to 22.09)
Pressure ulcer incidence at 14 d, No. (%)	30 (15.3)	34 (17.0)	NA	0.90 (0.56 to 1.42)
Heel, sacrum, or other	29 (14.8)	30 (15.0)	NA	1.00 (0.82 to 1.22)
Wrist	1 (0.5)	4 (2.0)	NA	0.25 (0.03 to 2.16)
Delirium duration during ICU stay, d	2.0 (1.6 to 2.5)	2.4 (1.9 to 2.8)	−0.4 (−0.9 to 0.2)	NA
Duration of ICU stay, d	14.0 (11.1 to 16.9)	11.3 (8.4 to 14.1)	2.7 (−0.4 to 6.0)	NA
ICU mortality, No. (%)	51 (26.0)	58 (29.0)	NA	0.96 (0.66 to 1.40)
Duration of hospital stay, d[e]	26.1 (20.4 to 31.7)	19.0 (13.5 to 24.6)	7.0 (1.3 to 13.6)	NA
Mortality at 90 d, No. (%)	73 (37.2)	82 (41.0)	NA	1.00 (0.72 to 1.40)
Functional, cognitive, and posttraumatic stress outcomes at 90 d				
Mini-Mental State Examination score[f]	26.1 (24.9 to 27.3)	26.5 (25.2 to 27.8)	−0.4 (−1.8 to 0.9)	NA
Altered cognition (score ≤24), No./total No. (%)	10/46 (21.7)	7/37 (18.9)	NA	1.11 (0.47 to 2.60)
Frontal Assessment Battery score <15, No./total No. (%)[g]	11/44 (25.0)	9/37 (24.3)	NA	1.07 (0.48 to 2.21)
Impact of Event Scale-Revised score ≥33, No./total No. (%)[h]	12/51 (23.5)	11/40 (27.5)	NA	0.91 (0.47 to 1.76)
Functional Independence Measure[i]	115 (109 to 121)	118 (112 to 124)	−2.92 (−9.38 to 3.45)	NA

Abbreviations: ICU, intensive care unit; NA, not applicable.

[a] Hazard ratios were used for ICU and hospital mortality, risk ratios for all other dichotomized outcomes.

[b] Cumulative dose of haloperidol, levomepromazine, and cyamemazine.

[c] Scores range from 0 (no mobilization) to 4 (ambulating).

[d] Unintentional withdrawal of invasive vascular (central venous, arterial, or dialysis catheters), urinary, or drainage devices.

[e] Determined for 191 patients in the low-use group and 193 patients in the high-use group.

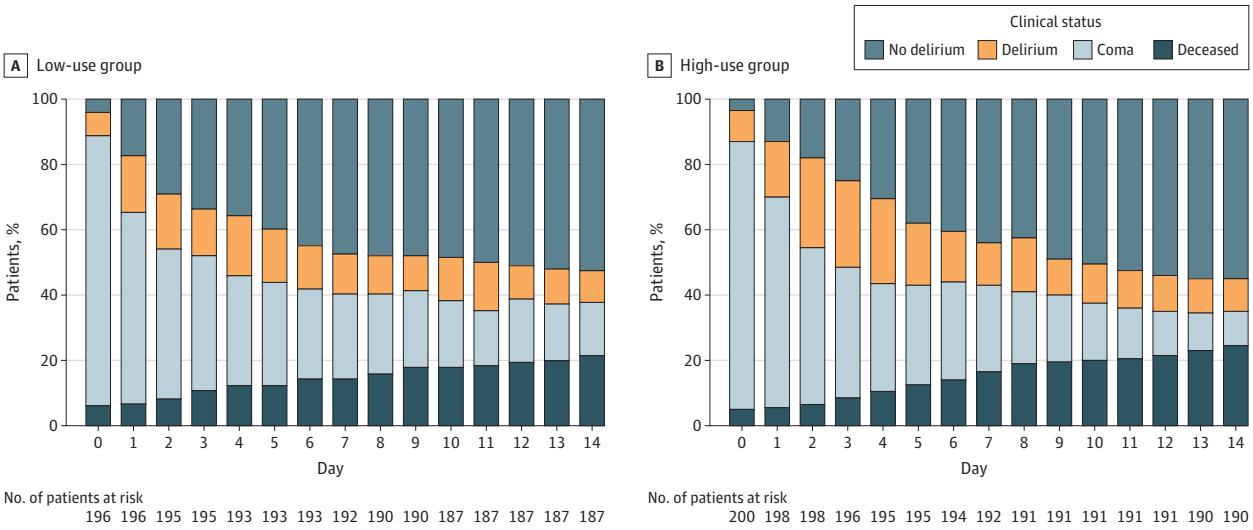
[f] Scores range from 0 to 30, with higher scores indicating better cognition. Scores determined for 46 patients in the low-use group and 37 patients in the high-use group.

[g] Scores range from 0 to 18, with higher scores indicating better executive function.

[h] Scores range from 0 to 88, with higher scores indicating greater posttraumatic stress symptoms.

[i] Scores range from 18 to 126, with higher scores indicating greater functional independence. Scores determined for 79 patients in the low-use group and 61 patients in the high-use group.

Figure 2. Component Bar Graph of Clinical Status During the 14-Day Intervention Period



Each bar represents the proportion of patients at the end of each study day, according to neurologic status: death, coma (RASS score of −4 or −5), delirium (CAM-ICU positive), or no delirium (RASS score greater than −4 and a negative CAM-ICU). Assessments were performed twice daily, from randomization through day 14. Stacked bars show the distribution of these mutually exclusive states over time. CAM-ICU indicates Confusion Assessment Method for the Intensive Care Unit; RASS, Richmond Agitation-Sedation Scale.

domization, Simplified Acute Physiology Score II, presence of COVID-19, and admission type (Figure 3B). For example, among patients with COVID-19, the mean number of days alive without delirium or coma at 14 days was 3.98 days in the low-use group vs 3.51 days in the high-use group, respectively (adjusted mean difference, 0.47 days [95% CI, -2.00 to 2.94]; P = .86). The per-protocol analysis, weighted per-protocol analysis, and post hoc subgroup analysis excluding patients who remained comatose throughout the ICU stay (up to 14 days) showed results similar to the primary analysis (eTable 8 in Supplement 1).

Discussion

In this multicenter randomized clinical trial of adult patients receiving invasive mechanical ventilation in the ICU, a low-use wrist-strap physical restraint strategy did not significantly increase the number of days alive without delirium or coma during the first 14 days after randomization, compared with a high-use strategy. These findings were consistent across all subgroups and were accompanied by similar rates of delirium, self-extubation, unplanned device removal, pressure ulcers, and day-90 mortality, as well as comparable exposure to sedative, analgesic, and antipsychotic agents. Functional, cognitive, and posttraumatic stress outcomes at 90-day follow-up were similar.

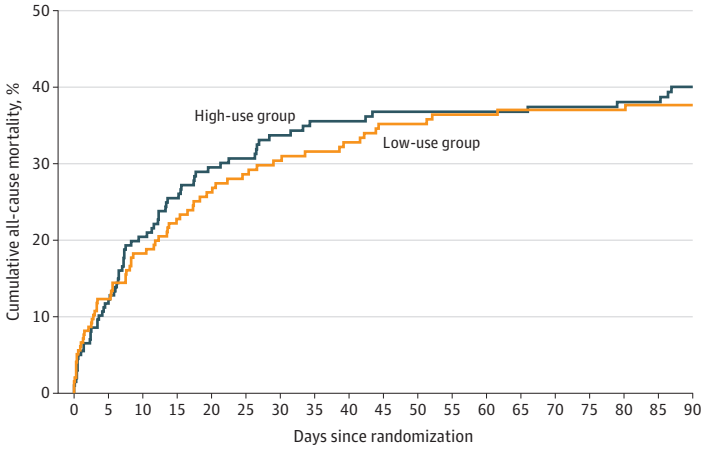
To the study investigators' knowledge, this is the first multicenter randomized clinical trial to directly compare 2 physical restraint strategies in patients receiving mechanical ventilation in the ICU. Existing recommendations on the use of physical restraints to maintain patient safety in the ICU rely largely on expert opinion and low-quality evidence.[1,27] This trial provides robust, high-quality data obtained in the general ICU population. The primary outcome—days alive without delirium or coma—has been shown to be strongly associated with both short- and long-term functional and cognitive outcomes in patients in the ICU.[10,11] The study was rigorously conducted, with standardized management of sedation, analgesia, and delirium screening. Other important outcomes after critical illness, including functional status, cognition, and posttraumatic stress, were also investigated.[28]

The absence of a measurable benefit in delirium- or coma-related outcomes does not exclude potential advantages of a restrictive approach to physical restraints in the ICU in other domains that were not captured in this trial, such as ICU recall[29] or the prevalence of stressful memories[30] among patients and their relatives. Alternatively, any potential benefit of a restrictive strategy on coma or delirium may have been smaller than anticipated or offset by competing mechanisms. Of note, in this population of patients who were severely ill, coma or delirium may be predominantly driven by common systemic factors rather than restraint exposure.[31] The absence of benefit should also be interpreted in light of nonadherence and outcome variability. Deviations from the assigned strategy may have diluted potential effects, while the dispersion of delirium- and coma-related outcomes may have limited the ability to detect small between-group differences.

Differences in safety outcomes, such as self-extubation, unplanned device removal, or agitation-related events, were not observed. These findings indicate that a low-use physical restraint strategy can be applied safely when integrated within a standardized approach to analgesia and sedation.[1] Moreover, the absence of differences in sedative prescription and achieved sedation levels suggests that a low-use wrist-strap strategy can be implemented, on average, without the need for escalation of sedative therapy.

Figure 3. Survival Curve of Mortality and Forest Plot of Subgroup Analyses of the Primary Outcome

A Cumulative all-cause mortality by group

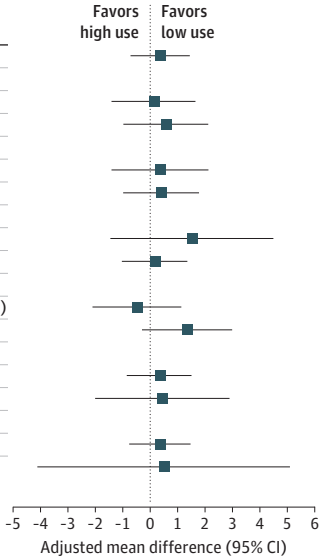


No. of patients at risk

High-use group	200	166	142	131	121	116	108	105	104	102	101	101	101	101	100	100	97	95	88
Low-use group	196	165	146	135	125	121	117	114	112	108	108	103	103	102	102	101	100	99	96

B Subgroup analyses

Subgroup	No. of patients		Mean No. of days alive without delirium or coma at 14 d (95% CI)		Adjusted mean difference (95% CI)
	Low-use group	High-use group	Low-use group	High-use group	
All patients	196	200	6.67 (5.69 to 7.65)	6.30 (5.35 to 7.24)	0.37 (-0.71 to 1.46)
Age, y					
<65	101	99	6.53 (5.31 to 7.75)	6.37 (5.16 to 7.58)	0.16 (-1.37 to 1.69)
≥65	95	101	6.81 (5.54 to 8.09)	6.23 (5.00 to 7.46)	0.58 (-0.97 to 2.13)
Sex					
Female	68	83	6.96 (5.55 to 8.36)	6.58 (5.29 to 7.88)	0.38 (-1.40 to 2.15)
Male	128	117	6.47 (5.30 to 7.64)	6.05 (4.89 to 7.22)	0.42 (-0.97 to 1.81)
Coma					
No	24	30	8.17 (5.96 to 10.38)	6.64 (4.66 to 8.62)	1.53 (-1.43 to 4.50)
Yes	172	170	5.72 (4.90 to 6.55)	5.53 (4.70 to 6.36)	0.19 (-0.98 to 1.36)
SAPS II score					
<45	112	106	6.84 (5.51 to 8.16)	7.31 (5.95 to 8.67)	-0.47 (-2.08 to 1.14)
≥45	84	94	6.96 (5.66 to 8.25)	5.60 (4.38 to 6.81)	1.36 (-0.28 to 3.00)
COVID-19					
No	158	164	7.02 (6.01 to 8.02)	6.65 (5.68 to 7.62)	0.37 (-0.81 to 1.55)
Yes	38	36	3.98 (2.09 to 5.88)	3.51 (1.58 to 5.44)	0.47 (-2.00 to 2.94)
Admission type					
Medical	188	182	6.66 (5.66 to 7.65)	6.27 (5.31 to 7.24)	0.38 (-0.75 to 1.51)
Surgical	8	18	7.15 (3.27 to 11.03)	6.65 (3.97 to 9.32)	0.51 (-4.11 to 5.12)



A, Cumulative incidence of death for the low-use and high-use strategy groups in the as-randomized population. B, Prespecified and exploratory subgroup analyses for the primary outcome—days alive without delirium or coma at 14 days—comparing the low-use and high-use strategy groups. The point estimates represent the adjusted mean differences between groups with corresponding 95% CIs. Subgroups were defined according to age (<65 vs ≥65 years; adjusted for coma only), sex, presence of coma at randomization (adjusted for age only), severity of illness (SAPS II score <45 vs ≥45), presence of COVID-19 at ICU admission, and admission type (medical vs surgical). No significant heterogeneity of treatment effect was observed across subgroups (*P* values for interaction > .10). ICU indicates intensive care unit; SAPS II, Simplified Acute Physiology Score II.

Limitations

This trial has limitations. First, the trial was open label, and assessment of the primary outcome was not blinded. It was not feasible to blind physical restraints at the bedside without compromising routine ICU care in participating centers. Second, patients' subjective memories of their critical illness were not assessed, which might have provided insight into the psychological effects of restraint exposure. Third, the study did not assess the effect of low- or high-use physical restraint strategies on families or health care professionals. Prior research suggests restraint use and patient agitation may contribute to increased workload, stress, and depressive symptoms.[32] Fourth, the workload of the clinical team was not measured. It is possible that although no differences were observed in safety events, the low-use strategy resulted in higher workload at the bedside. Fifth, the assessment rate for functional, cognitive, and posttraumatic stress outcomes was incomplete, and could not be performed systematically across

all centers because of organizational constraints and the COVID-19 pandemic. Sixth, these findings may not be generalizable to all ICU patients. Several high-risk populations, such as those with an active restraint order, delirium, dementia, or neurologic diagnoses at baseline, were excluded. Results may also differ in ICUs with other nurse staffing for patients receiving mechanical ventilation.[33]

Conclusions

Among adult patients receiving mechanical ventilation in the ICU, a low-use wrist-strap physical restraint strategy compared with a high-use strategy did not reduce days free of delirium or coma at 14 days.

ARTICLE INFORMATION

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