

# A bidimensional early intervention strategy of standard of care in combination with corticosteroids in elderly patients with mild to moderate COVID-19 (BEAT-COV study): a multicentre, open-label, randomized controlled trial

Received: 1 December 2025

Accepted: 16 January 2026

Published online: 06 March 2026

Cite this article as: Ruan Q., Zhang Y., Zhao T. *et al.* A bidimensional early intervention strategy of standard of care in combination with corticosteroids in elderly patients with mild to moderate COVID-19 (BEAT-COV study): a multicentre, open-label, randomized controlled trial. *BMC Infect Dis* (2026). <https://doi.org/10.1186/s12879-026-12637-8>

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1 **A bidimensional early intervention strategy of standard of**  
2 **care in combination with corticosteroids in elderly patients**  
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4 **multicentre, open-label, randomized controlled trial**

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45

**46 ABSTRACT****47 Background**

48 Elderly adults are at high risk for severe coronavirus disease 2019  
49 (COVID-19). Whether the use of corticosteroids in this population  
50 with mild to moderate COVID-19 could prevent disease progression  
51 remains controversial.

**52 Methods**

53 The BEAT COV trial assessed corticosteroids treatments in elderly  
54 patients with mild to moderate COVID-19. Eligible patients were  
55 randomly allocated (1:1) to either the intervention group (oral  
56 corticosteroids in combination with standard of care (SOC)) or the  
57 control group (SOC alone). Non-randomized patients were enrolled  
58 in an observational cohort. The primary outcome was the rate of  
59 severe or critical COVID-19 within 28 days.

**60 Results**

61 The study was terminated prematurely due to low COVID-19  
62 prevalence and decreasing severe cases, leading to an  
63 underpowered sample size. A total of 344 patients were screened,  
64 193 patients were randomly allocated to receive corticosteroids in  
65 combination with SOC (95 patients) versus SOC alone (98 patients),  
66 151 patients were included in the observational cohort. In the full  
67 analysis set (FAS) population, 1 (1.09%) patient in the corticosteroid

68 group and 4 (4.17%) patients in the SOC group developed severe or  
69 critical COVID-19 within 28 days (relative risk 0.26 [95% confidence  
70 interval {CI} 0.03–2.29];  $p=0.3688$ ). Similar findings were observed  
71 in the per-protocol (PP) population. One (0.75%) patient in the  
72 observational cohort developed severe COVID-19 within 28 days. All  
73 the adverse drug reactions (ADRs) were mild.

#### 74 **Conclusions**

75 In elderly with non-severe COVID-19, the use of corticosteroids  
76 combined with SOC did not significantly reduce the incidence of  
77 severe or critical COVID-19 compared to SOC alone. And the  
78 treatment shows a favorable safety profile. The study is exploratory  
79 in nature due to insufficient power, and given the limited evidence,  
80 further studies with larger sample sizes are warranted.

81 (Trial registration: ClinicalTrials.gov identifier, NCT05855395,  
82 registered on [2023-05-11]  
83 (<https://clinicaltrials.gov/ct2/show/NCT05855395>)).

84 **Keywords:** mild to moderate COVID-19, corticosteroids, standard of  
85 care, elderly patients, antiviral therapy.

86  
87

88

89 **Introduction**

90 On 5 May 2023, the World Health Organization (WHO) declared that  
91 COVID-19 was no longer a Public Health Emergency of International  
92 Concern. Even though the number of deaths and hospitalizations has  
93 significantly declined due to the widespread availability of vaccines  
94 and other public health measures, some regions are still  
95 experiencing localized outbreaks and transmission [1]. According to  
96 the data provided by US Center for Disease Control and Prevention  
97 (CDC), in the 2024-25 season, the overall rate of COVID-19-  
98 associated hospitalization was 15.1 per 100,000 people and weekly  
99 death rates due to COVID-19 were less than 3.8%. However, the  
100 elderly have the highest hospitalization rates among all age groups  
101 [2]. Similarly, a study from China showed that the overall rate of  
102 severe or critical illness in 2022 was as low as 0.035% [3]. However,  
103 this aggregate data masks the elevated risk for elderly populations,  
104 particularly amid persistent transmission chains driven by  
105 asymptomatic carriers. Presumably now, the asymptomatic subjects  
106 potentially contribute to the transmission of COVID-19 without their  
107 knowledge, intention, or being diagnosed as carriers [4]. As "silent  
108 spreaders", asymptomatic carriers may be highly infective during  
109 the incubation period [5]. Elderly individuals, due to their weaker  
110 immune systems and higher prevalence of underlying diseases, face  
111 a higher risk of infection after exposure to asymptomatic [6]. Once  
112 infected, this vulnerability translates to severe outcomes: about 4.4%

113 of elderly experienced severe to critical COVID-19 [7]. These results  
114 suggest that although the overall rates of COVID-19-associated  
115 hospitalizations and deaths may be relatively low, the elderly remain  
116 at higher risk, highlighting the need for targeted interventions and  
117 enhanced healthcare strategies to protect this vulnerable group.  
118 China has an elderly population of 190 million, accounting for 13.5%  
119 of the total population [8]. Protecting this vulnerable population  
120 (elderly patients) from severe or critical COVID-19 continues to be  
121 very important.

122 Studies have demonstrated that cytokine storm plays a critical role  
123 in the severe COVID-19 patients [9]. It might result in uncontrollable  
124 inflammation that further leads to multiple-organ failure, eventually  
125 leading to death [10-16]. Anti-inflammatory and immunosuppressive  
126 agents are considered effective therapeutic options for alleviating  
127 systemic inflammation [17]. Corticosteroids, interleukin-6 (IL-6)  
128 inhibitors, and tocilizumab have been utilized in severe patients [18].  
129 Nevertheless, prior studies evaluating corticosteroids in patients  
130 with mild to moderate COVID-19 have not reached a consensus, as  
131 noted in the discussion. Additionally, there is still inconsistency in  
132 guidelines along with a notable lack of robust evidence on the  
133 effectiveness of corticosteroids in preventing progression and  
134 reducing mortality [18,19]. Here, we report the results of this trial  
135 evaluating corticosteroids for elderly with mild to moderate COVID-  
136 19, aiming to determine whether corticosteroids reduce disease

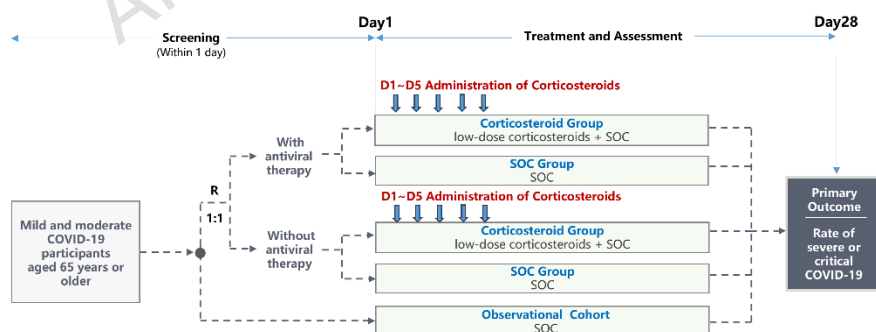
137 progression risk.

## 138 **Methods**

### 139 **Study design and participants**

140 BEAT COV is a multicentre, open-label, randomized, controlled trial  
 141 to evaluate the efficacy of corticosteroids in combination with SOC  
 142 in elderly with mild to moderate COVID-19. This trial was conducted  
 143 across 15 hospitals in China, including 14 large central hospitals and  
 144 one community healthcare center. Written informed consent was  
 145 obtained from all participants or their legal representatives before  
 146 screening. The study commenced on May 26, 2023, but was  
 147 terminated prematurely on November 30, 2024, due to the low  
 148 prevalence of COVID-19 and the declining incidence of severe cases.  
 149 The study design is provided in Figure 1.

150 **Figure 1. Study design schema**



151

152 Patients aged at least 65 years were eligible for the randomized  
 153 cohorts if they met the following criteria: (1) a positive SARS-CoV-2  
 154 test within 7 days prior to screening; (2) severity of mild or moderate

155 COVID-19 (mild COVID-19 is defined as respiratory symptoms,  
156 including but not limited to dry throat, sore throat, cough, and fever;  
157 moderate COVID-19 is defined as a). persistent fever lasting more  
158 than 3 days with (or without) symptoms, the respiratory rate (RR) is  
159 less than 30 breaths per minute, and the arterial oxygen saturation  
160 (SpO<sub>2</sub>) is greater than 93% on room air; or b). imaging findings may  
161 show characteristic signs of pneumonia due to SARS-CoV-2 infection)  
162 [20]; (3) initial COVID-19 symptom onset no more than 7 days before  
163 enrollment; (4) no systemic corticosteroid treatment in the previous  
164 seven days; (5) at least one of the following criteria: a. body  
165 temperature  $\geq 38^{\circ}\text{C}$ , b. c-reactive protein (CRP)  $\geq 27$  mg/L [21], or c.  
166 radiological findings indicative of pneumonia due to SARS-CoV-2  
167 infection; (6) no contraindications to systemic corticosteroids; and (7)  
168 willingness to receive systemic corticosteroids.

169 Patients were ineligible if they had (1) severe or critical COVID-19,  
170 (2) serious and uncontrolled medical status, (3) a life expectancy of  
171 less than 1 month, or (4) any other circumstances that, in the opinion  
172 of the investigator, are inappropriate for participation in the study.

173 If patients do not meet the key inclusion criteria (5), (6), and (7), but  
174 satisfy all other inclusion criteria and do not meet any exclusion  
175 criteria of the study, they will be enrolled in the observational cohort.

176 Incorporating participants who did not meet randomization criteria  
177 enhanced the population heterogeneity, thereby improving the  
178 external validity of findings. Furthermore, the observational cohort

179 design reflects real-world corticosteroid use in clinical practice.

## 180 **Randomization**

181 Patients were randomly assigned in a 1:1 ratio to receive standard  
182 of care plus corticosteroids or standard of care alone. Randomization  
183 was performed using block randomization to ensure an equal  
184 distribution of participants across groups. The randomization  
185 process involved creating blocks of participants, with each block  
186 containing an equal number of corticosteroid group and standard of  
187 care group allocations [22]. Meanwhile, randomization was stratified  
188 into two strata (one received antiviral therapy, the other one did not).  
189 Participants within each stratum will be randomized to ensure that  
190 everyone has an equal chance of being assigned to any treatment  
191 group within that stratum. This approach allows for the generation  
192 of two separate sets of randomization codes, one corresponding to  
193 the stratum with antiviral medication and the other to the stratum  
194 without antiviral medication. Randomization was performed using a  
195 sealed envelope technique for each stratum to ensure unbiased  
196 allocation of participants to the treatment groups. Randomization  
197 codes were generated by a random code generator before the start  
198 of the trial. These codes matched either the standard of care group  
199 or the corticosteroid group. Sealed envelopes containing the  
200 randomization assignments were prepared and sequentially labelled.  
201 Each envelope was opaque and tamper-proof to ensure that the  
202 randomization process remained concealed until the time of group

203 allocation. At the time of participants randomization at each site,  
204 eligible participant was allocated a randomly numbered envelope,  
205 which was opened by the investigator to reveal the treatment  
206 allocation.

## 207 **Procedures**

208 Randomized participants in the corticosteroid group received SOC  
209 in combination with corticosteroids (dexamethasone 3 mg,  
210 prednisolone 20 mg, or methylprednisolone 16 mg) once daily for 5  
211 days, while the SOC group and the observational cohort received  
212 SOC alone. The SOC was determined at the discretion of the  
213 investigator and may or may not include antivirals and other  
214 effective symptomatic treatments.

215 The study consisted of a screening period of 24 hours, a 5-day  
216 treatment period, and a follow-up period of 28 days (Figure 1). Pulse  
217 oximeters and 14-day antigen test kits were provided to all  
218 participants upon enrollment with the home care patients required  
219 to conduct daily health monitoring through structured diary cards  
220 during the follow-up period. The trial team conducted serial  
221 telephone follow-ups with inpatients, who received daily vital sign  
222 assessments at the hospital (detailed procedures are described in  
223 supplementary materials).

## 224 **Outcomes**

225 The primary outcome was a composite of the rate of severe or critical  
226 COVID-19 within 28 days that included, 1)  $\text{SpO}_2 \leq 93\%$  on room air,  
227 2) emergency department visits or hospitalizations due to COVID-19  
228 progression (defined as lung imaging showed significant progression  
229 more than 50% within 24~48 hours, or respiratory failure required  
230 mechanical ventilation, or shock) and with or without complication  
231 (associated with organ failure that require Intensive Care Unit [ICU]  
232 monitoring and treatment).

233 Secondary outcomes included the proportion of participants with (1)  
234  $\text{SpO}_2 \leq 93\%$  on room air, (2) emergency department visits or  
235 hospitalizations due to COVID-19 progression, (3) time to negative  
236 conversion for nucleic acid or antigen, (4) percentage of patients  
237 who maintained SARS-CoV-2 negativity on day 14, (5) time to initial  
238 alleviation of all symptoms (defined as the date symptoms first  
239 reported as none or mild), (6) time to sustained recovery of all  
240 symptoms (defined as the date when symptoms were first reported  
241 as either none or mild and subsequently remained at none or mild  
242 until 14 days), (7) the duration of respiratory symptoms (defined as  
243 the presence of any respiratory symptoms [mild, moderate or  
244 severe]), (8) time to hospitalization or emergency department visit  
245 due to COVID-19 progression, (9) all-cause mortality, (10) duration  
246 of hospital admission due to any cause. All time-to-event analyses  
247 used the date of randomization as the baseline. Safety outcomes

248 included the incidence rates of ADR and serious adverse drug  
249 reactions (SADR) related to corticosteroids and antivirals.

### 250 **Sample size and statistical analysis**

251 The sample size calculation was based on primary outcome. Given  
252 the current availability of various antivirals and the changes in herd  
253 immunity following the COVID-19 epidemic, we estimated that the  
254 severe or critical disease rate among elderly is now approximately  
255 1%. It was assumed that this rate would be reduced by 70% in the  
256 intervention group. To achieve 80% power and a 0.05 two-sided type  
257 I error in a pairwise comparison against the control group, a sample  
258 size of 2,355 patients was determined for each randomized group.  
259 Additionally, considering a dropout rate of 10% and the fact that 90%  
260 of the enrolled participants meet the criteria for corticosteroid use,  
261 the study aimed to screen approximately 5815 patients.

262 In the statistical analysis, primary efficacy was evaluated in both the  
263 FAS and the per-protocol set (PPS), while other endpoints were  
264 assessed only in FAS. The FAS is defined as all participants who met  
265 the eligibility criteria and who were randomized to receive at least  
266 one dose of the study drug. The PPS population included patients  
267 who had received at least one dose of study drug, had available  
268 primary outcomes, adhered to corticosteroid regimens not  
269 exceeding 80% to 120% of the established protocol, and did not  
270 experience any major protocol deviations in the assessment of the

271 primary endpoint. All secondary efficacy outcomes were analyzed  
272 using the FAS. Subgroup analyses were also done for the primary  
273 endpoint.

274 To quantify the treatment effect, we used relative risk (RR) with 95%  
275 confidence intervals to compare outcomes between the intervention  
276 and control arms. The primary outcome was analyzed using a Chi-  
277 square test if the theoretical frequency in all cells was  $\geq 5$  to assess  
278 group differences. Otherwise, Fisher's exact test was used to assess  
279 group differences. And the 95% CI was estimated using the Clopper-  
280 Pearson method. The same methods used for the primary outcome  
281 were also applied to analyze the proportion of patients with SpO<sub>2</sub>  $\leq$   
282 93% on room air and the rate of emergency department visits or  
283 hospitalizations due to COVID-19 progression. For the secondary  
284 time-to-event outcomes, Kaplan-Meier (KM) estimates were  
285 calculated, with the 95% CI was estimated using the Brookmeyer-  
286 Crowley method and log-log transformation for normal  
287 approximation. Missing data were assumed to be Missing at Random  
288 (MAR) or Missing Completely at Random (MCAR). No imputation  
289 was performed to address the missing values. In addition, the  
290 descriptive analyses were conducted on the observational cohort.

291 Analyses of the primary outcome were performed in five subgroups:  
292 the use of antiviral medications, the presence or absence of risk  
293 factors, disease severity (mild/moderate), infection history (first vs.  
294 prior) and enrollment time. Statistical methods consistent with the

295 primary endpoint were used in the analysis.

296 The safety analysis was performed on the FAS population, and data  
297 were collected on the rate and severity of ADRs, including those  
298 leading to discontinuation of the study intervention and those  
299 resulting in death. Analyses were done with the statistical analysis  
300 software SAS 9.4.

## 301 **Results**

### 302 **Patients**

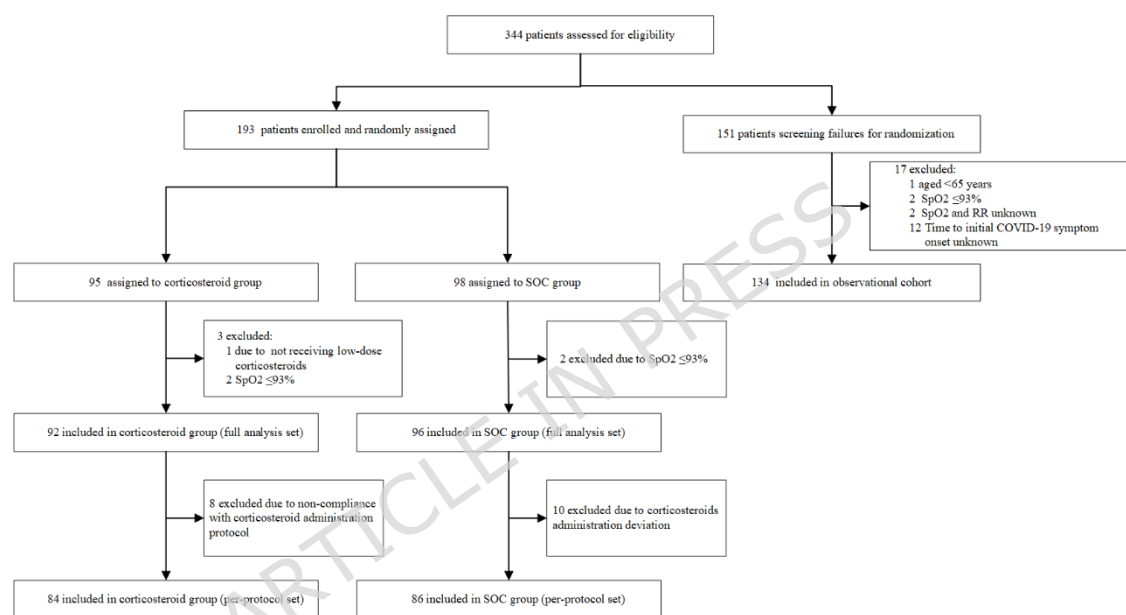
303 A total of 344 participants were screened from May 26, 2023,  
304 through September 10, 2024. One hundred ninety-three patients  
305 were randomized, of whom 95 were assigned to the corticosteroid  
306 group and 98 to the SOC group. One hundred and thirty-four patients  
307 were included in the observational cohort. The FAS set included 92  
308 patients in the corticosteroid group and 96 patients in the SOC group.  
309 Among the PP population, 84 patients were included in the  
310 corticosteroid group and 86 patients in the SOC group (Figure 2).  
311 The demographic and baseline characteristics are shown in Table 1.  
312 In the corticosteroid group, the median age was 71.0 years (IQR  
313 68.0–76.5), with 70 (76.1%) had received SARS-CoV-2 vaccination,  
314 60 patients (65.2%) had mild COVID-19, while 32 patients (34.8%)  
315 had moderate COVID-19. In the SOC group, the median age was 73.5  
316 years (IQR 68.0–78.0), with 69 (71.9%) had received SARS-CoV-2  
317 vaccination, 68 patients (70.8%) had mild COVID-19, while 28

318 patients (29.2%) had moderate COVID-19. Additional baseline  
 319 characteristics, as well as data on antiviral therapy and  
 320 corticosteroid use, are available in the Supplementary Material.

321 **Table 1. Demographic and Clinical Characteristics of the Full**  
 322 **Analysis Population at Enrollment**

323

324 **Figure 2. Trial profile**



325

326 **Primary Outcome**

327 In the FAS population, 1 (1.09%) of 92 patients progressed to severe  
 328 or critical COVID-19 in the corticosteroid group compared with 4  
 329 (4.17%) of 96 in the SOC group, and the rate of severe or critical  
 330 COVID-19 within 28 days was not significantly different between the  
 331 corticosteroid group and the SOC group (relative risk, 0.26; 95% CI,  
 332 0.03 to 2.29;  $p = 0.3688$ ). Notably, the wide 95% confidence interval

333 (0.03 to 2.29) for the relative risk in the FAS should be interpreted  
334 in the context of limited statistical power, which may be attributed  
335 to the small number of events (1 case in the corticosteroid group vs.  
336 4 cases in the SOC group). Results were similar in the PP population  
337 (1.19% vs. 2.33%; relative risk, 0.51; 95% CI, 0.05 to 5.54; p=1.0000)  
338 (Table 2).

## 339 **Table 2 Primary and Secondary Outcomes**

340

### 341 **Secondary Outcomes**

342 For secondary outcomes, there were no significant differences  
343 between the corticosteroid group and the SOC group concerning  
344 several key outcomes. In the FAS population, the proportion of  
345 patients with SpO<sub>2</sub> ≤ 93% on room air was 0% in the corticosteroid  
346 group compared to 4.17% in the SOC group (p=0.1213). Additionally,  
347 in the FAS population, the rates of emergency department visits or  
348 hospitalizations were 1.09% (due to respiratory failure required  
349 mechanical ventilation) in the corticosteroid group versus 0% in the  
350 SOC group (p=0.4894) (Table 2). On day 14, 98.8% of patients in the  
351 corticosteroid group and 97.6% in the SOC group tested negative for  
352 SARS-CoV-2. One death was reported in the SOC group within 28  
353 days, involving a patient who died after exiting the study, with the  
354 cause of death being unknown (Table 3).

355 All ADRs were associated with antivirals, and no ADRs related to the

356 corticosteroids (Table 4).

357 **Table 3 Additional Secondary Outcomes**

358 **Table 4: Adverse Drug Reactions**

359 **Subgroup Analyses**

360 Patients enrolled in 2023 and those enrolled in 2024 were compared.  
361 Patients enrolled in 2024 exhibited a significantly lower rate of  
362 severe or critical COVID-19 compared to those enrolled in 2023 (0%  
363 vs. 3.35%,  $p=0.0353$ ) (Table S6). Regarding the prior history of  
364 COVID-19 infection, 6 (4.08%) of 147 participants in the first  
365 infection group experienced severe or critical COVID-19 compared  
366 to 0 (0%) of 175 in the prior infection group, indicating a significant  
367 difference between the two groups ( $p=0.0086$ ) (Table S7). Additional  
368 subgroup analyses results are provided in the Supplementary  
369 Material.

370 **Discussion**

371 This randomized controlled trial evaluated the effect of  
372 corticosteroids on disease progression. Early termination resulted in  
373 insufficient statistical power and failure to reach the predetermined  
374 sample size. No significant difference was observed in progression  
375 to severe or critical COVID-19 within 28 days between the  
376 corticosteroid group and the SOC group. In addition, the RR has a  
377 wide confidence interval (95%CI 0.03–2.29), which indicates that the  
378 existing data cannot determine the potential benefits or risks of the

379 intervention. Consequently, current evidence is inadequate to  
380 support or refute the routine use of corticosteroids for this indication.  
381 The result is inconclusive due to several factors. First, this trial only  
382 enrolled in a limited number of subjects and has insufficient  
383 statistical power to detect significant differences between the  
384 treatment groups. Secondly the overall progression rates are low  
385 across the study cohorts. Existing studies have shown that the  
386 symptoms associated with the Omicron variant are generally milder,  
387 especially among vaccinated individuals [23-26]. In addition, the use  
388 of antivirals may further contribute to the low progression rate [26].  
389 According to previous studies, adults with mild to moderate viral  
390 diseases who receive antivirals earlier can have a lower chance of  
391 developing severe disease [27, 28]. In this study, over 90% of  
392 patients in the randomized cohorts received antivirals, and the  
393 widespread use of antivirals may be associated with the low rate of  
394 progression to severe or critical disease in COVID-19 patients. It  
395 should be noted that the rate of severe or critical COVID-19 in the  
396 randomized cohort (4.17% in the SOC group) was significantly  
397 higher than that in the observational cohort (0.75%), suggesting that  
398 the randomized cohort may have been enriched with high-risk  
399 individuals (meeting criteria of (a) body temperature  $\geq 38^{\circ}\text{C}$ , or (b)  
400 c-reactive protein (CRP)  $\geq 27$  mg/L, or (c) radiological findings  
401 indicative of pneumonia due to SARS-CoV-2 infection). Since such  
402 patients were excluded from the observational cohort, this risk

403 stratification difference may explain the higher rate of severe or  
404 critical COVID-19 in the randomized group. In this high-risk  
405 subgroup, the corticosteroid group showed a trend toward reduced  
406 the risk of severe disease (RR=0.26, 95%CI 0.03-2.29). Although the  
407 difference did not reach statistical significance (p=0.3688), these  
408 findings provide preliminary evidence supporting the potential  
409 clinical value of corticosteroid in this high-risk subgroup, and further  
410 verification of their definitive efficacy is warranted in large-scale  
411 randomized controlled trials.

412 Up to now the role of corticosteroids in preventing COVID-19  
413 progression is still unclear. Results from existing studies are  
414 controversial. Some studies on inhaled corticosteroids have  
415 indicated potential protective effects in preventing severe COVID-19.  
416 The STOIC trial included patients aged 18 and older with COVID-19,  
417 focusing on COVID-19-related emergency department visits as the  
418 primary endpoint. The study data indicated that short-term  
419 treatment with budesonide may effectively treat adults with early  
420 COVID-19, leading to a 91% relative reduction in clinical  
421 deterioration [29]. The PRINCIPLE trial included individuals aged 65  
422 and older or those aged 50 and older with comorbidities who were  
423 PCR positive or had suspected COVID-19 symptoms. The budesonide  
424 group demonstrated a reduction in COVID-19-related  
425 hospitalizations and mortality rates (6.8% vs. 8.8%, OR=0.75) and a  
426 shortened recovery time [30]. However, in the subgroup findings in

427 the RECOVERY trial, mortality was higher in the dexamethasone  
428 group than in the SOC group in patients not receiving oxygen (20%  
429 vs. 17%, RR=1.19, 95% CI 0.92-1.55), suggesting that  
430 dexamethasone may not be an effective treatment option for patients  
431 not receiving oxygen and may potentially increase the risk of death  
432 [31]. In our study, one patient in the SOC group died after  
433 withdrawing from the study, with the cause of death remains unclear.  
434 Nevertheless, when using corticosteroids in patients not receiving  
435 oxygen, clinicians still need to carefully assess the potential risks  
436 and benefits.

437 In the subgroup analysis according to enrollment time, all the  
438 subjects that progressed to severe or critical COVID-19 were  
439 enrolled in 2023, and there were none with progression in patients  
440 enrolled in 2024. These findings also suggest decreasing overall  
441 disease severity caused by COVID-19 over time. This trend is  
442 consistent with hospitalization rates reported by the CDC in the  
443 United States, which shows rates of 1.1%-7.8% in 2023 and 1.0%-2.9%  
444 in 2024 [32]. We also find that all cases of severe or critical disease  
445 occurred in patients with a first infection, all of whom were enrolled  
446 in 2023. This suggests that natural immunity from prior infection  
447 may provide greater protection against severe disease, consistent  
448 with previous reports.

449 Corticosteroids are known to reduce lung injury and systemic  
450 inflammation and alleviate symptoms such as fever [31]. The

451 PRINCIPLE trial indicated that the recovery time in the budesonide  
452 group was 11.8 days compared to 14.7 days in the SOC group  
453 (HR=1.21). Another study found that clinical recovery was 1 day  
454 shorter in the budesonide group compared with the usual care group  
455 (p=0.007) [30]. However, in our study, the time to initial alleviation  
456 of all symptoms and time to sustained recovery of all symptoms were  
457 similar between the corticosteroid group and the SOC group. This  
458 might be attributed to confounding factors: (1) the predominantly  
459 mild to moderate baseline symptoms in participants, which shorten  
460 the natural recovery window; and (2) the high prevalence of antiviral  
461 use (>90% in both arms), potentially accelerating symptom  
462 resolution and obscuring intergroup differences.

463 In this study, one patient in the corticosteroid group and one in the  
464 SOC group had persistently positive results in nucleic acid or antigen  
465 tests during the 14-day testing period. Six patients in this study  
466 showed antigen reversion to be positive after the seventh day of  
467 follow-up (4 in the SOC group, 1 in the corticosteroid group and 1 in  
468 the observational cohort). Despite no significant delays in the  
469 corticosteroid group observed, these results should be interpreted  
470 with caution due to the limited sample size.

471 All ADRs associated with antivirals observed in this study included  
472 mild gastrointestinal discomfort, pruritus and vomiting. These  
473 results are consistent with safety data reported in previous studies  
474 [33-35], indicating that these ADRs are relatively common and

475 usually mild, making them manageable reactions during antiviral  
476 treatment. While this study did not identify any significant safety  
477 concerns, clinicians should remain vigilant about the well-  
478 established risks associated with corticosteroid therapy (e.g.,  
479 immunosuppression, metabolic disturbances). It is recommended  
480 that a benefit-risk assessment be individualized according to each  
481 patient's characteristics.

482 This trial has notable limitations. Only 189 participants were  
483 enrolled in the randomized cohorts, reducing statistical power and  
484 limiting subgroup analyses, which hinders a comprehensive  
485 assessment of treatment effects. The open-label design potentially  
486 biased the objectivity of assessing subjective symptom outcomes.  
487 Specifically, the duration of respiratory symptoms in the  
488 Corticosteroids group (10.0 days) was longer than that in the SOC  
489 group (8.0 days), which is inconsistent with the expected anti-  
490 inflammatory effect of corticosteroids. This discrepancy may be  
491 attributed to assessors applying stricter criteria for symptom  
492 resolution in the corticosteroid group. Despite these limitations,  
493 objective indicators (e.g., time to nucleic acid negativity) showed no  
494 significant differences among the three groups, suggesting that the  
495 open-label design had a limited impact on the main conclusions. The  
496 wide confidence intervals observed for key outcomes (e.g., 0.03–2.29  
497 in the FAS and 0.05–5.54 in the PP population) reflect limited  
498 statistical power, primarily due to the low event rate of

499 severe/critical COVID-19 in both groups. This highlights the need for  
500 larger-scale studies to confirm these findings. And for safety  
501 endpoints, only ADRs related to corticosteroids and antivirals were  
502 collected. Lastly, the lack of collected viral genotypes limits the  
503 assessment of SARS-CoV-2 mutations and their potential impact on  
504 patient prognosis.

505 Conclusively, as this study is exploratory in nature due to insufficient  
506 power, it did not demonstrate that combining oral corticosteroids  
507 with SOC could decrease the rate of progression to severe or critical  
508 disease within 28 days among elderly with mild to moderate COVID-  
509 19. However, corticosteroids demonstrated a good safety profile in  
510 this population.

511

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512 **Declarations**

513 **Author contributions**

514 W.H.Z., Q.L.R., J.Q.W., and F.S. designed the study and led this study.  
515 T.T.Z. wrote the trial protocol. Y.L.Z., X.L., R.C., Y.Z.L., F.Z., X.Q.Z.,  
516 W.S., J.W.G., D.M.Z., Y.Y.L., L.Y.Z., C.W., Y.B.L., X.C.D., F.L.H., and  
517 L.Y.S. were responsible for subject enrollment and clinical data  
518 collection. T.T.Z. wrote the first draft of this manuscript, with  
519 conceptual guidance from W.H.Z., Q.L.R., and J.Q.W. on the  
520 interpretation of the findings. All authors had full access to all the  
521 data in the study and had final responsibility for the decision to  
522 submit for publication.

523

524 **Funding**

525 This work was supported by National Key Research and  
526 Development Program of China [2023YFC3043400], and Shanghai  
527 Sci-Tech Inno Center for Infection & Immunity [SSIII-202402].

528

529 **Acknowledgements.**

530 We would like to thank the health workers and the staff at the  
531 participating health facility for supporting this work. We are also  
532 deeply grateful to all members of the project team for their  
533 invaluable contributions. Finally, we acknowledge the participating  
534 institutions for providing research resources.

535

536 **Data availability**

537 Complete data are available upon request from the corresponding  
538 author.

539

540 **Ethics approval and consent to participate**

541 The protocol and all amendments were approved by the ethics  
542 committees of Huashan Hospital (Study Number 2023-065) and its  
543 collaborating hospitals. Written informed consent was obtained from  
544 all participants or their legal representatives before screening. All  
545 patient data were treated with strict confidentiality, and records  
546 were anonymized for analysis. All procedures involving human  
547 participants in this study were conducted in accordance with the  
548 ethical standards of the institutional and national research  
549 committees, and in full compliance with the principles outlined in the  
550 1964 Declaration of Helsinki and its subsequent amendments.

551

552 **Consent for publication**

553 Not applicable.

554

555 **Competing interests**

556 All authors declare that they have no conflicts of interest.

557

558

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714 **Table 1. Demographic and Clinical Characteristics of the Full Analysis Population at Enrollment**

<b>Characteristic</b>	<b>Corticosteroids (N=92)</b>	<b>SOC (N=96)</b>	<b>Observational cohort (N=134)</b>
<b>Age</b>			
No.	92	96	134
65-79 — no. (%)	76(82.6)	76(79.2)	104(77.6)
>=80 — no. (%)	16(17.4)	20(20.8)	30(22.4)
Median age (IQR) yr	71.0(68.0–76.5)	73.5(68.0–78.0)	72.0(68.0–78.0)
<b>Sex — no. (%)</b>			
No.	92	96	134
Male	40(43.5)	44(45.8)	69(51.5)
Female	52(56.5)	52(54.2)	65(48.5)
<b>Smoking history— no. (%)</b>			
No.	91*	96	134
Non-smokers	85(93.4)	89(92.7)	121(90.3)
Current smokers (smoking > 5 cigarettes/day in the past 3 months)	1(1.1)	2(2.1)	6(4.5)
Current smokers (smoking ≤ 5 cigarettes/day in the past 3 months)	2(2.2)	0	1(0.7)
Former smokers (not smoking in the past 3 months)	3(3.3)	5(5.2)	6(4.5)

<b>Characteristic</b>	<b>Corticosteroids (N=92)</b>	<b>SOC (N=96)</b>	<b>Observational cohort (N=134)</b>
<b>Vaccination status — no. (%)</b>			
No.	92	96	134
Unvaccinated	22(23.9)	27(28.1)	37(27.6)
Vaccinated	70(76.1)	69(71.9)	97(72.4)
<b>History of previous COVID-19 infection — no. (%)</b>			
No.	92	96	134
Unknown	1(1.1)		
No	42(45.7)	51(53.1)	54(40.3)
Yes	49(53.3)	45(46.9)	80(59.7)
<b>COVID-19 severity — no. (%)</b>			
No.	92	96	134
Mild	60(65.2)	68(70.8)	125(93.3)
Moderate	32(34.8)	28(29.2)	9(6.7)
<b>Days from the onset of COVID-19 symptom to first dose— no. (%)</b>			
No.	92	96	134
>72 hours	36(39.1)	37(38.5)	32(23.9)

<b>Characteristic</b>	<b>Corticosteroids (N=92)</b>	<b>SOC (N=96)</b>	<b>Observational cohort (N=134)</b>
≤72 hours	56(60.9)	59(61.5)	102(76.1)
Other high-risk factors for COVID-19† — no. (%)			
No.	92	96	134
No	20(21.7)	29(30.2)	43(32.1)
Yes	72(78.3)	67(69.8)	91(67.9)
Immunological disorders or currently requiring immunosuppressive treatment— no. (%)	1(1.1)	1(1.0)	0
Cardiovascular diseases (including hypertension) no. (%)	56(60.9)	47(49.0)	68(50.7)
Chronic liver disease— no. (%)	4(4.3)	5(5.2)	5(3.7)
Chronic pulmonary disease— no. (%)	10(10.9)	10(10.4)	9(6.7)
Chronic kidney disease— no. (%)	4(4.3)	6(6.3)	5(3.7)
Cancer— no. (%)	12(13.0)	10(10.4)	12(9.0)
Diabetes— no. (%)	18(19.6)	16(16.7)	26(19.4)
Maintenance dialysis— no. (%)	1(1.1)	0	0
Obesity (BMI≥30kg/m <sup>2</sup> )— no. (%)	2(2.2)	3(3.1)	1(0.7)

<b>Characteristic</b>	<b>Corticosteroids (N=92)</b>	<b>SOC (N=96)</b>	<b>Observational cohort (N=134)</b>
Heavy smokers <sup>‡</sup> — no. (%)	3(3.3)	7(7.3)	10(7.5)
Patient setting — no. (%)			
No.	92	96	134
Inpatients	55(59.8)	55(57.3)	40(29.9)
Outpatients	37(40.2)	41(42.7)	94(70.1)

715 \*One patient was excluded due to unknown smoking status within the past three months.

716 †High-risk factors other than age.

717 ‡Heavy smokers is defined as smoking  $\geq$  400 cigarettes per year.

718 Note: Baseline characteristics were assessed at enrollment.

719 **Table 2 Primary and Secondary Outcomes**

Outcome	Full Analysis Set				Per-protocol analysis			
	Corticosteroids (N=92)	SOC (N=96)	p-value	Relative risk (95% CI) <i>No./total No. of patients (%)</i>	Corticosteroids (N=84)	SOC (N=86)	p-value	Relative risk (95% CI)
<b>Primary outcome</b>								
Severe or critical COVID-19 within 28 days*	1/92 (1.09)	4/96 (4.17)	0.3688	0.26 (0.03-2.29)	1/84 (1.19)	2/86 (2.33)	1.0000	0.51 (0.05-5.54)
<b>Secondary outcomes</b>								
Severe COVID-19†	0	4/96 (4.17)	0.1213	..	0	2/86 (2.33)	0.4971	..
Critical COVID-19‡	1/92 (1.09)	0	0.4894	..	1/84 (1.19)	0	0.4941	..

720 \*Defined as progression to severe or critical status or death within 28 days.

721 † Criteria for progression to severe status are referenced from the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection (Trial Version 10)."

722 ‡ Criteria for progression to critical status are referenced from the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection (Trial Version 10)."

723 Note: The low event rate in this analysis limits the statistical inference of the results.

724

725 **Table 3 Additional Secondary Outcomes**

	<b>Corticosteroids</b>	<b>SOC</b>	<b>Observational cohort</b>	<b>Hazard ratio#</b>
	<b>(N=92)</b>	<b>(N=96)</b>	<b>(N=134)</b>	<b>(95% CI)</b>
Percentage of patients who maintained SARS-CoV-2 negativity on day 14— no. (%) §	85(92.4)	87(90.6)	127(94.8)	..
All-cause mortality— no. (%)	NA	1(1.04)□	NA	..
Median (IQR) negative conversion time for nucleic acid or antigen, days	4.0(3.0-6.0)	4.0(3.0-5.0)	4.0(3.0-5.0)	0.89(0.66-1.20)
The median time to initial alleviation of symptoms, days	2.0(1.0-3.5)	2.0(1.0-3.0)	2.0(1.0-3.0)	0.95(0.66-1.36)
The median time to sustained recovery, days	2.0(1.0-4.0)	2.0(1.0-4.0)	2.0(1.0-3.0)	0.94(0.66-1.35)
The median duration of respiratory symptoms, days	10.0(5.0-14.0)	8.0(5.0-12.0)	5.0(3.0-9.0)	..
The median time to hospitalization or emergency department visit due to COVID-19 progression	NA	NA	NA	..

	<b>Corticosteroids</b>	<b>SOC</b>	<b>Observational cohort</b>	<b>Hazard ratio#</b>
	<b>(N=92)</b>	<b>(N=96)</b>	<b>(N=134)</b>	<b>(95% CI)</b>
The median duration of hospital admission due to any cause	NA	NA	NA	..

726 #Hazard ratios were calculated using a Cox proportional-hazards model. A hazard ratio was evaluated between participants receiving corticosteroids  
727 and those receiving SOC.

728 §No significant difference was observed in the percentage of patients maintaining SARS-CoV-2 negativity on day 14 between the corticosteroid group  
729 and the SOC group.

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730 **Table 4: Adverse Drug Reactions**

	<b>Corticosteroids (N=92)</b>	<b>SOC (N=96)</b>	<b>Observational cohort (N=134)</b>
ADR— no. (%)	1	0	2
Mild ADR	1(1.09)	0	2(1.49)
Moderate ADR	0	0	0
Sever ADR	0	0	0
ADRs related to corticosteroid	0	0	0
ADRs related to antiviral medication	0	0	0
ADRs leading to discontinuation of the study intervention	0	0	0
SADR	0	0	0
ADRs resulting in death	0	0	0

731 An adverse drug reaction is defined as any adverse drug reaction occurring or worsening relative to the baseline from the first dose of the study drug  
732 to day 28.

