JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.955434
J Contemp Med 2022;12(2):211-216

Orijinal Araştırma / Original Article

Administering Geriatric Pneumonia Cases without Waiting for CRP Results, is It Practicable?

Geriatrik Pnömoni Vakalarının CRP Sonuçları Beklenilmeden Yönetimi Pratik Olur Mu?

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Abstract

Aim: C-reactive protein (CRP) is a notable marker of many diseases. Accordingly, in most cases, the clinical management of infectious diseases is revised based on CRP alterations. This study thus attempted to predict CRP alterations via immature granulocyte count (IGC) and nucleated red blood cell count (NRBC) in a geriatric population with pneumonia.

Materials and Methods: We carried out our study in the intensive care unit of a private hospital by retrospectively reviewing the laboratory findings of geriatric patients with pneumonia and an age-matched control group in the same ICU.

Results: In total, we reviewed 495 hospitalization days (the summed amount of days all 43 patients) and 221 hospitalization days (the summed amount of days all 20 controls) records. In the group comparisons, we found a statistical significance in the patient group for both IGC (p=0.001) and NRBC (p=0.002) increase. Comparing IGC to CRP measures from the following day and the day after that, there was a statistical significance in IGC increase (p=0.001) but not in NRBC (p=0.156). Further, IGCs below 0.3×103 and above 0.5×103 were better able to predict CRP alterations.

Conclusion: In geriatric patients with pneumonia, IGC is more effective than NRBC in predicting CRP variations before their actual occurrence, with the mean estimation time at least 2 days prior.

Keywords: CRP variability, geriatric pneumonia, Immature granulocyte count, Intensive care unit, Nucleated red blood cell count

Öz

Amaç: C-Reaktif Protein (CRP) birçok hastalık için önemli bir belirteçtir. Buna göre, çoğu vakada, bulaşıcı hastalıkların klinik yönetimi, CRP değişikliklerine dayalı olarak revize edilir. Dolayısıyla bu çalışma, pnömonili geriatrik popülasyonda immatür granülosit sayısı (İGS) ve çekirdekli eritrosit sayımı (ÇE) yoluyla CRP değişikliklerini öngörmeye çalışmıştır.

Gereç ve Yöntem: Özel bir hastanenin yoğun bakım ünitesinde yatan geriatrik pnömonili hastaların ve yaş uyumlu bir kontrol grubunun laboratuvar bulgularını retrospektif inceleyerek çalışmamızı gerçekleştirdik.

Bulgular: Toplamda, 495 hastanede yatış gününün (43 hastanın toplam yatış gün sayısı) ve 221 hastanede yatış gününün (20 kontrolün toplam yatış gün sayısı) kayıtlarını inceledik. Grup karşılaştırmalarında hasta grubunda hem İGS (p=0.001) hem de ÇE (p=0.002) artışı için istatistiksel anlamlılık bulduk. Ertesi gün ve ondan sonraki gün İGS ile CRP ölçümleri karşılaştırıldığında, İGS artışında (p=0.001) istatistiksel anlamlılık vardı, ancak ÇE'de (p=0.156) yoktu. Ayrıca, 0,3×103'ün altındaki ve 0,5×103'ün üzerindeki İGS'ler, CRP değişikliklerini daha iyi tahmin edebildiler.

Sonuç: Pnömonili geriatrik hastalarda, İGS, ortalama tahmin süresi en az 2 gün önce olmak üzere, CRP değişimlerini tam oluşmadan önce tahmin etmede ÇE'den daha etkilidir.

Anahtar Kelimeler: CRP değişimi, çekirdekli eritrosit sayısı, geriatrik pnömoni, immatür granülosit sayısı, yoğun bakım

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Received *(Geliş Tarihi)*: 22.06.2021 **Accepted *(Kabul Tarihi)*:** 21.12.2021

INTRODUCTION

Pneumonia is an acute, severe respiratory disease characterized by airflow limitations due to inflammation. [1] It is associated with significant morbidity and mortality in the geriatric population.[1] Besides a clinical evaluation, laboratory tests are useful for determining prognosis in pneumonia treatment. In the geriatric population, however, this may not be entirely consistent, as these patients are prone to insufficient immune responses.[2]

C-reactive protein (CRP) is an annular-shaped protein produced by the liver that indicates inflammation in the human body.[3] It was named after a matter that reacts with the somatic capsular polysaccharide antibody, and its half-life is less than 24 hours.[4] As a component of the acute phase response, CRP correlates with inflammation. Despite these qualities, elevations or reductions in CRP due to inflammation and disease severity sometimes do not follow a similar course. In these cases, precursor substances, such as procalcitonin, may evaluate disease progress instead.[5] However, the adequacy of the procalcitonin is not reliable in oncological or thrombotic events.[6]

Aside from changes in CRP, due to infection severity, there are also changes in the proportion of the granulocyte series, which can begin to appear in the peripheral blood as well. These changes are evidence that the bone marrow is under stress. Accordingly, immature granulocyte (IG) are one of the initial products of an activated immune system reaction, and it is typical to see IG in the peripheral blood in severe infectious or inflammatory processes.[7] IG count (IGC) can then allow us to have an idea of an inflammatory state like a peripheral blood smear.

Related, nucleated red blood cell count (NRBC) forms the precursor erythrocytes that respond to hypoxic stress, such as acute hemolytic crises, hematologic malignancies, and severe infections.[8] Detecting NRBC in adults is pathological and directly reflects excessive erythropoietic activity.[9] The shape of the cells in NRBC is quite similar to that of lymphocytes, though, and because of this similarity, automatic cell counting devices often add NRBC to the number of lymphocytes. These results can thus be misinterpreted as lymphocytosis. At this point, NRBC is extremely important. It can help in disease diagnosis and treatment.[10,11] Both IGC and NRBC can be obtained from a complete blood count (CBC) result.

CRP has guided us many times in the treatment of infections. However, CRP alterations may not be estimated precisely from clinical patient signs, as CRP level might have already changed by the time clinical tests take place.[12] This situation causes delays in treatment modality adjustments, mainly in geriatric patients who have impaired immunity. [13] It is therefore helpful to those patients to estimate CRP's alteration time. IGC, NRBC and CRP are similar inflammation markers, thus, we feel that IGC and NRBC can contribute to this estimation as much as clinical findings in pneumonia cases. As such, an early laboratory prediction based on IGC and NRBC can prove beneficial in the treatment of groups with delayed immune responses.

There is not enough research on geriatric pneumonia cases in the intensive care unit (ICU). Furthermore, there is not enough data on geriatric patients with pneumonia in the ICU regarding specifically IGC, NRBC, and CRP in the literature. As such, this study aims to predict CRP alterations in geriatric pneumonia ICU cases just before the actual CRP change.

MATERIAL AND METHOD

This retrospective study was conducted at a private hospital in 2019. The local university ethical committee approved the study protocol. The study was conducted according to the Declaration of Helsinki. An agreement was obtained from the private hospital to evaluate the patients' data prior to the study.

Geriatric patients with bacterial or viral pneumonia treated in the ICU and an age-matched group with normal CRP were included in this study. The patients were chosen according to the International Classification of Disease (ICD-10) codes, including J18 (Pneumonia) and A41 (other sepsis) (14). These selected codes covered the severe clinical spectrum for the patients with pneumonia in the ICU. In addition, the clinical pneumonia was confirmed by the radiological reports of the patients. Patients with oncologic, traumatic, or neurologic diagnoses were excluded from the evaluation. We also checked the patients' daily follow-up charts to determine unexpected clinical abnormalities such as intubation, fever, and hypotension. Per the follow-up charts, patients with a point of less than 5 on the Glasgow coma scale on the day of admission were excluded as well.[15] Patients receiving steroids during hospitalization were not featured in the study. Further, we were sure to include patients who used similar drugs during their treatment.

The control group consisted of patients hospitalized in the ICU due to non-infectious diseases (diabetes mellitus, cerebrovascular disease). The same exclusion criteria were applied to the control group, and daily laboratory results and medications were also noted.

The participants' laboratory tests which were studied with the Sysmex Xn-1000 AHA and Beckman Au 2700 branded devices from January to May 2019 were obtained from the hospital's archived electronic database. Initially, we chose patients who had been tested for both CBC and CRP every day. We primarily included the CRP and CBC laboratory records, which were studied more than once a day to estimate the CRP deviation time on an hourly basis. As shown in **Figure1,** the IGCs and NRBCs gathered the day before the CRPs were compared.

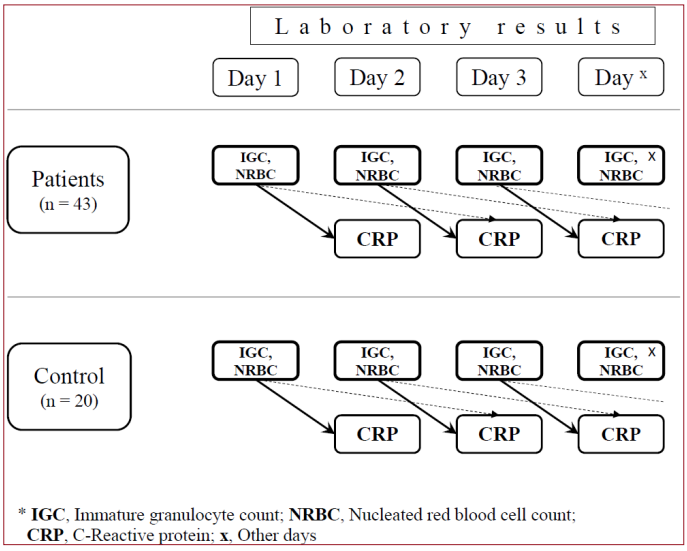

Figure 1. Study design.

Statistical Analysis

The statistical analyses were performed using SPSS ver. 21 (SPSS Inc., Chicago, IL, USA). Pearson's correlation was used to compare normally distributed data, whereas for non-normal data, the Spearman correlation was used. A one-way ANOVA test was used in the continuous multi-group analysis for normally distributed data. A post hoc (Bonferroni) test was performed to indicate the differences between participant groups. For categorical variables, we used the chi-square test. An independent samples t-test was applied to identify the significance between groups and continuous data, while A linear regression test was performed for the correlations between the patients IGCs and the CRP results of the following day (day 2) and the next day after tomorrow (day 3). We accepted a value of $p<0.05$ as statistically significant.

RESULTS

At first, we reviewed 65 files for the from the first 5 months of 2019. Nine of the records reported that the corresponding patients had been hospitalized for less than 3 days (we evaluated at least three hospitalizations days results), while 13 of them had incomplete clinical data. In the control group, 35 files were reviewed. Fifteen of them could not pass over the exclusion criteria. Finally, we reviewed 495 patient hospitalization days (the summed amount of days all 43 patients) and 221 control hospitalization days (the summed amount of days all 20 controls) records were included in the study. The patients did not use common drugs other than acetylsalicylic acid, antihypertensives, proton pump inhibitors, oral antidiabetics, analgesics, and inhalers. Additionally, none of them were given oral or intravenous steroids during treatment. All the patients' renal and liver functions were normal per their age, and their O2 saturations were at least > 80%. The patients' and controls' demographic information and laboratory results are detailed in **Table 1**.

Table 1. Demographics and laboratory results of patients and control groups

	Patients (n = 43)	Control group (n = 20)	P values
Mean age	78±9.6	76±3,4	0.121
Gender, F/M	20/23	10/10	0.210
Hospitalization day, n	11.51±6.39	5.8±3.1	0.042
Cause of hospitalization	COPD*, Pneumonia	DM†, CVD‡	NA§
Laboratory results			
WBC¶, $\times 10^9$/L	14.07±7.16	7.29±1.13	0.001
ANC†‡, $\times 10^9$/L	(0.63-91.3)	(2.09-5.82)	0.001
ALC††, $\times 10^9$/L	(0.08-11.4)	(1.55-3.31)	0.001
CRP†§, mg/L	(1.32-166.4)	(15.1-63.4)	0.001
IGC¶†, $\times 10^3$/uL	(0.01-2.96)	(0.05-0.05)	0.001
NRBC¶‡, $\times 10^3$/uL	(0-15)	(0-0.01)	0.002

P values are the comparison of patient and control groups. (Chi-Squared test or Mann Whitney U test); Data are the median, n (%), or n/N (%); *Chronic Obstructive Pulmonary Disease; †, Diabetes mellitus; ‡, Cerebrovascular disease; §, Not applicable; ¶, White blood cell; †‡, Absolute neutrophil count; ††, Absolute lymphocyte count; †§, C-Reactive Protein; ¶†, Immature granulocyte count; ¶‡, Nucleated red blood cell count.

Of the hospitalization days, only 41 days revealed normal CRP values. When the CRP variations from the remaining 454 days of total hospitalization were compared per IGC and NRBC, IGC was positively correlated with the CRP of the next day (r=0.224); NRBC was not. Further, IGC was positively correlated with the day after that as well (r=0.18). Similarly, another positive correlation existed between NRBC and both IG (r=0.158) and white blood cell (WBC) (r=0.179), as expected.

The next section of the evaluation was concerned with the comparison of the ICU patient and control groups. There was a statistical significance in the patient group for IGC (p=0.001, η=0.103) and NRBC (p=0.002, η=0.018). We compared the IGCs and NRBCs of the test day with the next days' CRP results. We found a significant difference in IGC (p=0.001, "Y=19.08*X+72.84") (**Figure 2a**), unlike NRBC (p=0.156). Even when we compared IGC with the CRP results of the day after that, they were still significant (p=0.006, "Y=15.40*X+73.63") (**Figure 2b**).

After that, we separated IGC into categories according to radio frequencies (%) and direct current (x 10^3 u/L) (16). Every category was ten times more numerous than the previous one. In brief, we formed a total of seven categories based on IGC results (**Figure 2c**). When we evaluated the IGC prediction degree of high-CRP levels (>5 mg/L), a one-way ANOVA revealed that groups 1-2 and 1-7 were more effective (F=5.049, p=0.001; **Figure 2d**). The lower IGC thus values seemed better able to predict high CRP. However, no significant differences were found at low CRP levels (<5 mg/L; p=0.121).

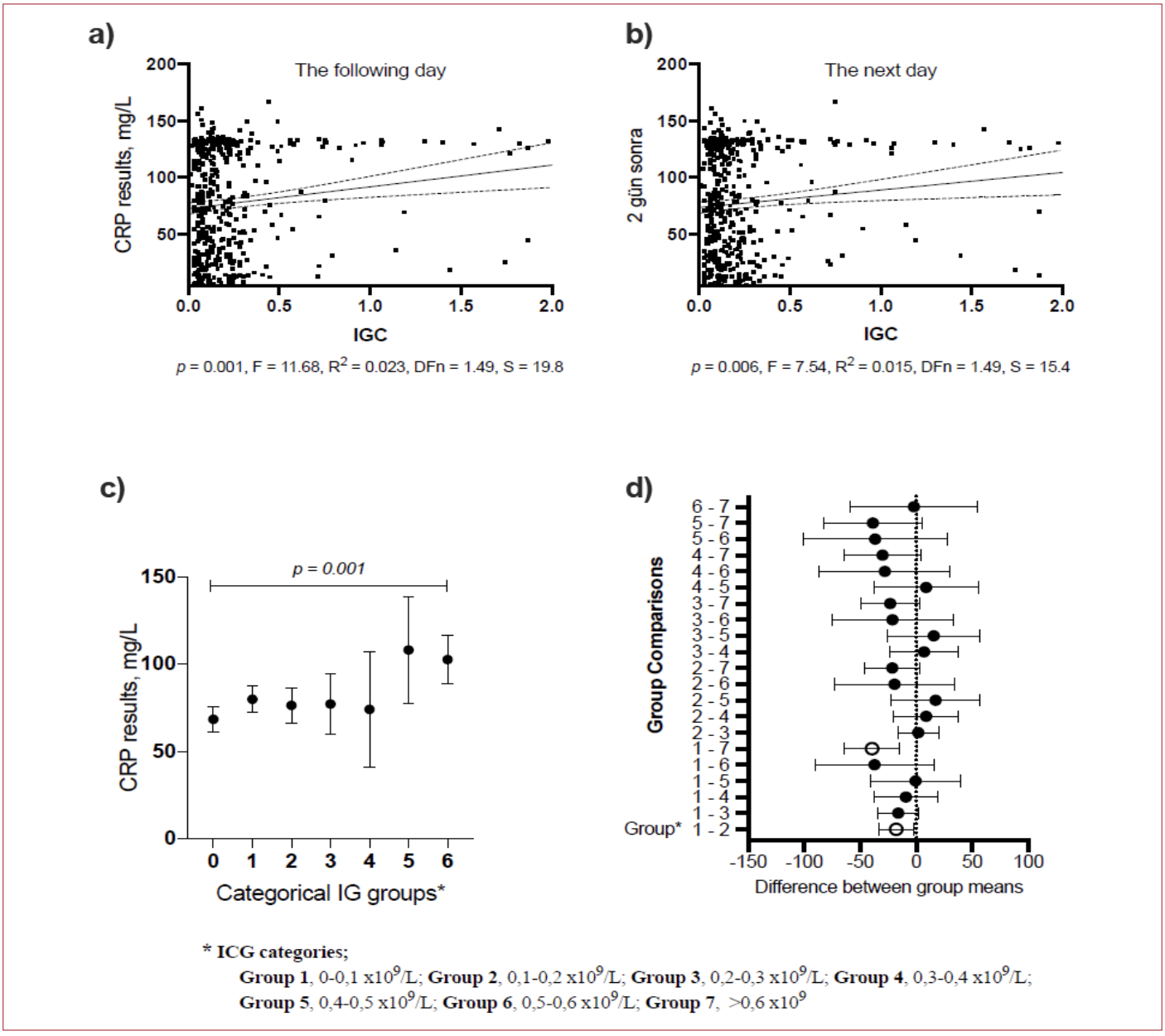

Figure 2. Comparisons between IGC subsets and C-Reactive Protein. a) Comparisons of patients' IGCs and the next day's CRP results; b) Comparison of patients' IGCs and CRP results from the next day; c) Patients' IGC categories according to radio frequencies; d) Comparisons of categorized IGC results and CRP values.

DISCUSSION

Our study's outcomes indicate that in geriatric ICU patients with pneumonia, IGC can predict CRP alterations at least one day before the actual change. Contrarily, NRBC does not make such predictions.

CRP has been used as an inflammatory marker of many diseases for almost a century.[3] However, because CRP's half-life is less than 24 hours, another inflammatory marker that can sooner alert medical professionals to a CRP alteration will improve patient treatment.[4] What is surprising from our results is that IGC not only gives information about the day it was measured, but also predicts the CRP values of the next day or even 2 days later (p=0.007). This means that IGC changes up to 2 days before the CRP alteration, and can help clinicians change patient treatment earlier than is possible through other clinical test predictions, as clinical progress predictability is vital in rapidly progressive diseases such as pneumonia.

A single-centered study showed that IGC is correlated with severe pancreatitis.[7] The study also revealed that an elevation in IGC estimates the degree of pancreatitis. The researchers confirmed IGC's estimation ability with high specificity and even labeled these cases as severe pancreatitis with increased IGC in the early hours. The use of the term hour is notable for the similarity to our present study, as one of its goals was to make inferences about CRP on an hourly basis. Our results ultimately revealed that IGC value changes predict CRP variation at least 24 hours before it actually occurs.

Another recent study also found that IGC indicates severe bacterial infection in children.[17] These researchers aimed to determine the effects of a marker in pediatric patients who came to the emergency department due to fever, and they noted that IGC was specific like WBC in bacterial infections. The inclusion of mild patients in their studies shows that IGC is important in the severity of different diseases. We did not classify the disease severity in our study, however, even a small amount of IGC in all disease levels could accurately predict the CRP variation at least 1 day in advance. This finding broadly supports the work of the related study and indicates that IGC is useful in demonstrating CRP in different age groups and disease levels.

An additional retrospective study analyzed the data of 204 patients who underwent an appendectomy and concluded that IGC was not as effective as WBC for diagnosis.[18] While IGC elevated with other infection markers, there was no correlation between these factors. However, the IGC results in the study were only registered to the first decimal unit when they should be calculated to the nearest thousandth to be considered relevant; thus, we noted our results in milliunits to observe more sensitivity. Accordingly, in our study, IGC was statistically significantly correlated to CRP predictions.

NRBC increase can be expected in bone marrow stress secondary to infection severity. Ballantine et al. compared NRBC rate, the need for blood transfusion, and the tendency for acute chest syndrome in patients with sickle cell disease.[19] In the study, an adequate number of patients were hospitalized due to vaso-occlusive crises. The patients' NRBC was found statistically significant in all compared stages. This study's importance stems from how these medical emergencies were caused by inflammation, not infection, that is, NRBC was associated with the inflammation process. In our infection-based study, the NRBC results correlated with the CRP results; however, NRBC failed to predict CRP variation. Our results are thus in agreement with this related study, indicating that NRBC does not affect infection, as it is likely to be concerned with red cell maturation.

Although the current study was based on a small patient sample, we examined how soon IGC can predict CRP deviation, not the patients' individual CRP responses. Therefore, we evaluated the number of total hospitalization days and CRP values alone, or about 500 days of data. Moreover, we evaluated patients who had three comorbidities (geriatric patients with pneumonia in the ICU), which caused the number of patients to be low. Still, our study was limited by the absence of enough blood samples on the same hospitalization day; thus, we could not reduce the CRP estimation time. Further studies can provide hourly information. Since most of the studies performed on NRBC are based on inflammation, additional NRBC research is also needed for infection cases.

According to our outcomes, we could predict changes in CRP before they occur, but not whether these changes increase or decrease at the stationary CRP states. Even so, the increase and decrease of CRP and IGC were concurrent, while for NRBC, this assumption was not clear. Overall, we can underline that the IG exchange starts at least 24 hours before the CRP exchange. This time can allow new treatment changes to take place, as geriatric patients cannot generate proper immune responses given usually insufficient CRP and WBC elevations.

CONCLUSION

This research's findings have several practical implications, though two are of particular interest. First, predicting the direction of CRP deviation sooner strengthens the current infection treatment of geriatric patients. Second, IGC can easily be integrated into a standardized method of analysis in most routine hemogram counting devices. In conclusion, the most apparent finding to emerge from this study is that IGC can detect CRP alterations at least 24 hours prior to the event actually occurring.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the ethical committee of Karatay University School of Medicine on 20.03.2019. (2019/007 numbered).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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