Stress and motivation of cell processing operators: A pilot study of an online questionnaire survey

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1. Introduction

While technological development of mechanization and automation is progressing in cell processing for regenerative therapy, flexibility is often required and, in many cases, cell processing is carried out manually by operators [1,2]. In particular, cell culture is a delicate process that relies heavily on the manual skills of the operators [3,4], and cell processing operators (CPOs) play an important role in ensuring the processing of cell products that maintain safety and quality. That is, CPOs are one of the most important human assets for the industrial development of regenerative therapy. However, the investigation of attributes, work environment, and psychological aspects of CPOs to take advantage of this important human asset has not been done. Thus, the objectives of the current study were, first, to investigate the attributes of CPOs, second, to identify the factors that give CPOs mental stress, and third, to identify the motivational factors of CPOs.

Methods: An online questionnaire was conducted to investigate the attributes of participants, stresses, and motivations; the questionnaire included multiple-choice questions. A survey questionnaire was distributed to 64 operators in 31 CPFs, including universities, clinics, and pharmaceutical companies, from December 2021 to February 2022. Participants responded to the online survey via Microsoft Forms.

Results: Approximately half of the CPOs had been employed for two years or less, and they were more likely to experience various stressful situations than CPOs with three or more years of experience. In particular, the wear of dust-free clothing and work in a unique environment of a clean room, where it is difficult to take breaks due to the nature of the closed space, were considered to be particularly stressful situations. However, these CPOs have high motivations based on their pride in being involved in cutting-edge medical care, which is highly expected by society, and in contributing to patient care.

Conclusions: While stress with training and education programs for CPOs is an issue that can be resolved through in-house training, other issues that are difficult to resolve immediately, such as mechanization to relieve the stress of human manual operations, were identified. Continued efforts to analyze and alleviate the stress factors identified in this study are expected to improve the quality of CPOs’ work and maintain the important human asset of CPOs.
CPOs in their work environment is important in maintaining this human asset. For example, cell culture for clinical transplantation must be conducted in a clean room, a special closed environment [7]; however, working in a closed space is a major form of stress [8,9]. These stresses can lead to work errors, decreased satisfaction, and eventually turnover [10,11]. Comparatively, society’s high expectations for regenerative therapy may contribute to motivation to work as a CPO [12,13]. To maximize CPO performance, it is necessary to identify the causes of stresses and sources of motivations.

Therefore, in the current study, an online survey was conducted to clarify what constitutes stress and motivation for CPOs. The objectives of the survey were, first, to investigate the attributes of CPOs, second, to identify the factors that give CPOs mental stress, and third, to identify the motivational factors of CPOs. Overall, this study analyzed the work environment of CPOs by focusing on their psychological aspects.

2. Methods

2.1. The survey questionnaire

An online questionnaire was designed by the authors to investigate the participants’ attributes, stresses, and motivations; this questionnaire used multiple-choice questions. Tables 1 and 2 show the details of the questionnaire to investigate stresses; these were single-choice questions. In the current study, frequency and degree were tabulated and participants’ responses, as per the asterisk choice shown in Table 3, were defined as high stress. Tables 4–6 show the details of the questionnaire about motivations and these were the top three multiple-choice questions. The items on the questionnaire and their responses were in Japanese. The English, translated-version of the items are presented in the tables.

2.2. Recruitment

A survey questionnaire was distributed to participants in 31 CPFs, including universities, clinics, and pharmaceutical companies

### Table 1

| B Personal skill | B1 I’m not sure if I did the disinfection and cleaning properly, as they are done by hand. |
|------------------|--------------------------------------------------------------------------------------------------|
| B2 I’m concerned about whether I am doing my cell culture technique properly. |
| B3 I’m worried about whether the final product will conform to the requirements. |
| B4 I’m worried that my work errors may cause deviations. |
| C Communication | C1 I feel uneasy working with beginners. |
| C2 I feel that the waiting time is too long due to conflicts with other work. |
| C3 I have to respond to sudden changes in the production schedule. |
| C4 I think the workload is too much for the number of workers in the CPF. |
| C5 There is an education and training system, but I feel that the content is insufficient. |

Asterisks* indicate significant differences by years of experience.

2.3. Statistical analysis

Statistically evaluated data were calculated with GraphPad Prism 9 (GraphPad Software, CA, USA). P values were calculated by Fisher’s exact test. Two-tailed P values of <0.05 were considered to be significant. Responses of “Not applicable,” such as not being in charge of the tasks in the question, were excluded from the statistical analysis. Each of the stress-related questions’ data reliability was assessed by calculating its Cronbach’s coefficient alpha.

3. Results

3.1. Participants’ attributes

There were 64 participants from 31 CPFs. Both males (n = 34, 53.1%) and females (n = 30, 46.9%) participated in the online survey (Fig. 1A). The age distribution of the participants was as follows: 42.2% were in their 30s, 29.7% were in their 40s, 14.1% were in their 20s or younger, and 14.0% were in their 50s (Fig. 1B). In the questionnaire about years of experience in CPF, operators with two years or less experience—defined as “beginner”—accounted for half of the participants (53.1%), while 46.9% were operators with three years or more experience—defined as “advanced” (Fig. 1C). The number of operators in the institutions ranged from 1 to 10, accounting for 46.9% of the total (Fig. 1D). The manufacturing sector accounted for 81.3% of the participants’ task type (Fig. 1E). Regarding certifications, 82.8% of the participants responded that it was not applicable and 17.2% were certified by JSRM. Advanced operators possessed certifications significantly higher than beginner operators (Fig. 1F; P = 0.002, Fisher’s exact test).

### Table 2

| Details of the questionnaire about stresses in a clean room. |
|------------------------------------------------------------|
| D Clothes in clean room d1* Clothes (dustless clothing, gloves, etc.) are uncomfortable due to poor ventilation. |
| d2 Clothes (dust-free clothing, goggles, etc.) make it difficult to work or operate. |
| E Environments in clean room e1* Noise from equipment, etc. is too loud. |
| e2 Concerned about people looking at me to double-check my work, presence of surveillance cameras, etc. during the operations. |
| e3 Unpleasant odor or irritation from chemicals used for cleaning or decontamination. |
| e4 The monotonous colors of the room and equipment make it difficult to concentrate. |
| F Conditions in clean room f1* It is difficult to take a break or rest after entering the CPF. |
| f2 Carrying goods into the CPF is complicated and time-consuming. |
| f3* Physical labor such as standing and cleaning before and after work causes fatigue. |
| f4 Inventory management is complicated due to lack of space for stocking inventory. |
| f5 Preparation and cleanup are more complicated than the culture operation. |

Asterisks* indicate significant differences by years of experience. Dagger $|$ shows the top three chosen items.
Regarding the environment in a clean room, beginner CPOs re-
motivations, while 9.1% had low motivations (Fig. 4A). 3.3. Motivations

dissati
communication suggested that beginner CPOs were signi-
experience was not a factor (Fig. 3B). Responses to the section on
were evaluated separately. In the personal skill analysis, years of
however, signi-
differ based on the participants
conditions in a clean room, dif
entering the CPF included the highest number of high-stress in-
in the questionnaire about con-
or higher, indicating a high data reliability. In the questionnaire
questionnaire about communications, no items were found to be
mistakes was a concern for most of the participants (Fig. 2B). In the
questionnaire about environments in a clean room, frustration was less
uncomfortable with its effect on operability (Fig. 2D). In the ques-
naire about clothes in a clean room, 63.9% of participants were
dominated by high-stressed individuals (Fig. 2C). In the question-
questionnaire included the highest number of high-stress in-
participants at 64.4% (Fig. 2F).

3.2. Stresses in clean room

Three-quarters of participants reported feeling stressed about working at CPFs (Fig. 2A). Each response to the items pertaining to personal skills, communications, and clothes, environments, and conditions in clean room had a Cronbach’s coefficient alpha of 0.9 or higher, indicating a high data reliability. In the questionnaire about personal skills, the possibility of deviation due to one’s own mistakes was a concern for most of the participants (Fig. 2B). In the questionnaire about communications, no items were found to be dominated by high-stressed individuals (Fig. 2C). In the questionnaire about clothes in a clean room, 63.9% of participants were uncomfortable with its effect on operability (Fig. 2D). In the questionnaire about environments in a clean room, frustration was less than in other categories (Fig. 2E). In the questionnaire about conditions in a clean room, difficulty in taking a break or rest after entering the CPF included the highest number of high-stress individuals at 64.4% (Fig. 2F).

Stress levels for operations within the CPF did not signifi-
cantly differ based on the participants’ years of experience (Fig. 3A); however, significant differences were observed when the items were evaluated separately. In the personal skill analysis, years of experience was not a factor (Fig. 3B). Responses to the section on communication suggested that beginner CPOs were significantly dissatisfied with their workload and training system (Fig. 3C). Regarding clothes in a clean room, beginner CPOs were stressed by the inconvenience of dustless clothing and gloves (Fig. 3D). Regarding the environment in a clean room, beginner CPOs reported stress from the noise of the equipment and the smell of the decontamination chemicals (Fig. 3E). Moreover, complaints about fewer break times or rest periods and high fatigue levels were strongly stressed by beginner CPOs (Fig. 3F).

3.3. Motivations

The 53.1% of the CPOs who participated in the survey had high
motivations, while 9.1% had low motivations (Fig. 4A). “Job
satisfaction” was the most frequently chosen source of motivation, followed by “Salary,” and “Pride of being involved in cutting-edge medical care,” respectively (Fig. 4B). Regarding moments of increased motivation, “When you achieve your goals” was chosen by 42.9%, followed by “When you realize that your work is leading to saving patients’ lives” and “When you are working on the job you want to do” (Fig. 4C). Comparatively, regarding moments of decreased motivation, 49.2% selected “When you make mistakes or failures,” followed by “When you have a bad relationship with others in the workplace” and “When you do not feel fulfilled in your work,” respectively (Fig. 4D).

| Table 3 |
| Definition of high-stress individuals. |
| Stress degree | Not applicable | No stress | Very low levels of stress | Slightly low levels of stress | Slightly high levels of stress | High levels of stress | Very high levels of stress |
|----------------|----------------|------------|--------------------------|-----------------------------|-----------------------------|------------------------|--------------------------|
| Stress frequency |               |            |                          |                             |                            |                        |                          |
| Think often.     | *              | *          | *                        |                             |                            |                        |                          |
| Sometimes.       |                |            |                          |                             |                            |                        |                          |
| Almost never.    |                |            |                          |                             |                            |                        |                          |
| I don’t think so. |                |            |                          |                             |                            |                        |                          |
| I used to think so, but now, I have become used to it. |                |            |                          |                             |                            |                        |                          |

Asterisks* represent the indicators of high-stress individuals as defined in this study.

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Stress levels for operations within the CPF did not significantly differ based on the participants’ years of experience (Fig. 3A); however, significant differences were observed when the items were evaluated separately. In the personal skill analysis, years of experience was not a factor (Fig. 3B). Responses to the section on communication suggested that beginner CPOs were significantly dissatisfied with their workload and training system (Fig. 3C). Regarding clothes in a clean room, beginner CPOs were stressed by the inconvenience of dustless clothing and gloves (Fig. 3D). Regarding the environment in a clean room, beginner CPOs reported stress from the noise of the equipment and the smell of the decontamination chemicals (Fig. 3E). Moreover, complaints about fewer break times or rest periods and high fatigue levels were strongly stressed by beginner CPOs (Fig. 3F).

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4. Discussion

In recent years in Japan, a number of new clinical studies have been conducted [14 – 16]. Moreover, various cell products are continuously approved. Currently, among 16 cell products approved until June 2022, 14 cell products are autologous tissue or cell derived products. Autologous cell products depend on the technique by CPOs to culture cells since each patient has a different condition. Therefore, CPOs are an important human asset for the future industrial development of regenerative therapy. However, the analysis of the work environment of these important human assets is unclear. In the current study, an online survey was conducted to clarify the attributes, stress, and motivations of CPOs to better understand their work environment.

4.1. Source of motivation

| Table 4 |
| Source of motivation. |
|----------------------|
| 4B b1* Job satisfaction |
| b2* Salary |
| b3 Work environment is right for me (working hours, location, benefits, etc.) |
| b4* Pride of being involved in cutting-edge medical care |
| b5 Fulfillment in private life and holidays |
| b6 Evaluation from colleagues and human relations |
| b7 Satisfaction with personal goals (skill development) |
| b8 Acquisition of certifications |
| b9 Recognition from family |
| b10 Promotion and salary increase (career advancement) |
| b11 Contribution to industrialization of regenerative medicine |
| b12 Others |

Asterisks* indicate the top three chosen items.

4.2. Moments of increasing motivation

| Table 5 |
| Moments of increasing motivation. |
|------------------|
| 4C c1 When someone thanks you. |
| c2* When you are working on the job you want to do. |
| c3* When you realize that your work is leading to saving patients’ lives. |
| c4* When you achieve your goals. |
| c5 When you have completed a difficult task. |
| c6 When you work together with your colleagues to complete your tasks. |
| c7 When you receive a salary commensurate with your achievements. |
| c8 When someone compliments you. |
| c9 When you receive a promotion or salary increase. |
| c10 Others |

Asterisks* indicate the top three chosen items.

4.3. Moments of decreasing motivation

| Table 6 |
| Moments of decreasing motivation. |
|------------------|
| 4D d1 When a complaint is received from outside the workplace. |
| d2 When you receive an unfair evaluation. |
| d3* When you have a bad relationship with others in the workplace. |
| d4* When you make mistakes or failures. |
| d5* When you do not feel fulfilled in your work. |
| d6 When the company/organization does not agree with your direction. |
| d7 When you work long hours or cannot take vacations. |
| d8 When you cannot achieve your goals. |
| d9 When you do not receive a salary that is commensurate with your achievements. |

Asterisks* indicate the top three chosen items.
The majority of certificated CPOs, accounting for 90.9% in this study, have more than three years of experience, suggesting that the certification system by JSRM is useful in shaping the career paths of CPOs. Comparatively, 53.1% of the participants had less than two years’ experience, indicating that many of the CPOs were inexperienced. This beginner CPOs were reported to have higher cross-contamination risk in manual operations than advanced CPOs. Therefore, the attribute of CPOs must be continuously investigated to clarify future trends of this important human asset.

A large percentage of the participants felt that the questions related to clothes and conditions in a clean room were highly stressful. These factors may be attributed to the psychological burden faced by CPOs due to human manual operations. Mechanization is considered in terms of cost, and it is estimated that the initial cost will be exceeded by the production of 33 or more batches of cell products per year [17]. However, the most commercially available cell products in Japan are still manufactured manually, although 200 have been sold, based on market size calculations. Although it may take time to achieve complete mechanization, it is hoped that equipment will be developed in the future to reduce the mental load derived from human manual operations.

Fig. 1. Attributes of participants. (A) Gender. (B) Age distribution. (C) Years of experience in CPFs. (D) Number of operators (%). (E) Task type. (F) Number of certifications and years of experience in CPFs. *P values were calculated by Fisher’s exact test.

Fig. 2. Ratio of high-stress individuals selecting items in the questionnaire about stresses. (A) Responses to items about high or low stress levels. (B) Ratio of high-stress individuals selecting items about personal skills. Items b1–b4 are detailed in Table 1. (C) Ratio of high-stress individuals selecting items about communication. Items c1–c5 are detailed in Table 1. (D) Ratio of high-stress individuals selecting the items about clothes in clean room. Items d1 and d2 are detailed in Table 2. (E) Ratio of high-stress individuals selecting the items about environments in clean room. Items e1–e4 are detailed in Table 2. (F) Ratio of high-stress individuals selecting the items about conditions in clean room. Items f1–f5 are detailed in Table 2.
Assuming that stress would be higher in an enclosed space, such as a clean room, we designed relevant questions for the online survey to investigate this. In the current study, stress related to the environment tended to be higher among inexperienced CPOs. They were particularly concerned about noise and the smell of chemicals used in decontamination. However, the stress felt in clean rooms is reduced in CPOs with three years or more experience. This difference in adaptation to a clean room environment according to years of experience may simply be habituation. Moreover, attitudes of positive acceptance and adaptation to special environmental conditions have also been suggested to be characteristics possessed by Japanese workers [18]. It is also conceivable, however, that only such CPOs can continue working for a long time; thus, ongoing research on stress among CPOs is necessary.

In other questions about stresses, it was revealed that inexperienced CPOs may be dissatisfied with communication, education,
and training. Therefore, support systems, such as systematically organized CPOs workshops, must be established to reduce dissatisfaction about communications. Continued efforts to analyze and reduce the stress factors identified in this study will help CPOs to improve the quality of their work.

More than half (53.1%) of the CPOs were found to have high motivations, which is higher than the proportion of nurses (50.4%) who considered their job, in itself, to be motivating [19,20]. In particular, these sources of motivation came from achieving their own goals and implementing what they wanted to do. The realization that they were saving patients’ lives was also an important factor in maintaining CPOs’ motivations. Thus, visualization of the contribution to society is a motivating factor for CPOs to be involved in cell production.

4.1. Limitations

In the current study, we faced a limitation in the restricted numbers of survey participants, since the total population of CPOs could not be established. This is because it is not clear how many people are involved in the work of CPOs, how many people are in single CPFs, and how many of these people hold certifications.

There are, however, two ways to estimate the total population of CPOs from the data obtained in this study. The first is to estimate this from the number of facilities: as of April 2022, the Ministry of Health, Labor and Welfare reports that there are 3263 CPFs in Japan. Since the median number of CPOs per CPFs was calculated to be 15 persons in this study, it can be estimated that there are currently 48,945 CPOs in Japan. The second method is to estimate this from the number of certifications. Assuming that the 17.2%, which is the percentage of certifications in this study, reflects the total population of CPOs, the number can be calculated to be 2697 CPOs, based on 464 certifications in 2022 as published by the JSRM. However, there are significant discrepancies in the respective estimates and ongoing research is needed to obtain more accurate data.

5. Conclusions

This study assessed attributes, stresses, and motivations of CPOs, an important human asset for the industrial development of regenerative therapy. Approximately half of the CPOs had been employed for two years or less and were more likely to experience various stressful situations than CPOs with three or more years’ experience. In particular, the wear of dust-free clothing and the various stressful situations than CPOs with three or more years employed for two years or less and were more likely to experience regenerative therapy. Approximately half of the CPOs had been an important human asset for the industrial development of

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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