

## Incidence of Hand-Foot Syndrome in Patients with Breast Cancer on Capecitabine Treatment

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## 1. Abstract

**1.1. Background:** Capecitabine is an oral prodrug used for the treatment of various cancer diseases. Capecitabine is activated to 5-FU. The most severe adverse effect is “hand-foot syndrome.

**1.2. Aim of the Study:** The aim of this study is to evaluate the incidence of hand-foot syndrome in breast cancer patients taking capecitabine.

**1.3. Methods:** This study was done at the Imam Hussein Oncology Center in Kerbala Province, Iraq, from July 2022 until December 2022. In this study, 100 female breast cancer patients participated. Particular forms were prepared to assess the incidence of hand-foot syndrome for each precipitated patient, plasma concentration of a particular drug, 5-FU, was calculated with the minister of science and technology; and an HPLC device was used to detect plasma concentration for each participant patient.

**1.4. Result:** The results obtained from this study indicated that 53% of patients in this center suffered from hand-foot syndrome, with a grade range of 1 to 3 and a plasma 5-FU concentration range of 301 to 393. Among the 53% of patients who participated in the study who experienced hand-foot syndrome, 37% had grade 1 symptoms, 12% had grade 2 symptoms, and 4% had grade 3 symptoms.

**1.5. Conclusion:** This study concludes that there is a correlation between adverse effects and 5-FU plasma concentrations.

## 2. Introduction

Cancer denotes a group of diseases characterized by uncontrolled and abnormal cell proliferation. A tightly regulated process of cell division, growth, and death ensures the correct functioning of tissues and organs in a healthy body. This control mechanism malfunctions in cancer, resulting in the formation of a mass of cells known as a tumor [1]. Breast cancer is the most prevalent malignancy among women worldwide, accounting for 25% of all cancers and an estimated 1.57 million new cases as of the most recent report. It is also the primary cause of cancer-related deaths among females [2]. With a 23% cancer-related mortality rate, breast cancer has become a significant threat to female health in Iraq, where it is the leading cause of death among women after cardiovascular disease [3]. Capecitabine was specifically designed for oral administration, to deliver 5-FU to the tumor site and to avoid systemic 5-FU exposure. Treatment with capecitabine consisted of 14 days of twice-daily oral capecitabine (1250 mg/m<sup>2</sup>) administered in 3-week cycles, followed by a 7-day recovery period. Oral capecitabine is highly effective for the management of breast and colorectal cancer [4]. By using a three-step enzymatic cascade, the innovative oral fluoropyrimidine carbamate capecitabine preferentially produces 5-fluorouracil (5-FU) in tumor tissue. The prodrug capecitabine is quickly and completely digested after being absorbed from the gastrointestinal tract in its intact form. It undergoes a three-step enzymatic cascade to become 5-FU. It is

first converted to 5'-deoxy-5-fluorocytidine (5'-DFCR) by hepatic carboxyl esterase. This is then changed to 5' deoxy-5-fluorouridine (5' DFUR) by the enzyme cytidine deaminase. Thymidine phosphorylase (TP) is an enzyme that changes 5' DFUR into 5-FU in both tumor and healthy tissues [5]. The most serious side effect of capecitabine is a hand-foot syndrome (HFS) [6]. Burning pain, together with clearly visible symmetric edema and erythema, may develop in 3–4 days. The hands are typically more frequently affected than the feet, and in some instances, they may even be the sole affected part. HFS can disrupt normal daily activities, particularly when blistering, moist erosions, excruciating pain, or ulceration appear. HFS is controllable, but if ignored, it can advance quickly. However, capecitabine dose reduction and cessation typically result in a swift improvement of signs and symptoms without negative long-term effects. Hand-foot syndrome is frequently brought on by inhibitors of several kinases and capecitabine [7]. The pathogenesis of hand food syndrome is toxic degradation of the epidermal barrier, which is consistent with the clinical and histological alterations found in HFS [8]. Additional indications of toxic harm include (1) dose-dependence, which has been documented for chemotherapy drugs like 5-fluorouracil, capecitabine, PLD, and cytarabine, as well as MKIs like sorafenib. (2) the occurrence becoming more frequent after exposure to the causative substance (such as with longer-term or continuous low-dose infusion therapies, liposomal preparations with a long half-life, or continuous). Regarding the pathogenetic mechanisms of injury, several hypotheses have been made: The areas of skin around the sweat glands have a high concentration of drug excretion from the sweat glands [9]. The toxic chemical leaks into the nearby tissue as a result of microtrauma to the capillaries at mechanically stressed sites [10]. Because the keratinocytes' relevant enzymes are very active, breakdown products from the harmful agent might build up in certain regions of the skin. For instance, more activity has been observed in the palms than in the skin on the back for the enzymes thymidine-phosphorylase (TP), which activates capecitabine, and dihydropyrimidine-dehydrogenase (DPD), which degrades 5-FU an [11].

### 3. Aim of the Study

Aim of the study is to evaluate the incidence of hand-foot syndrome in women taking capecitabine to treat breast cancer.

### 4. Methods

This study was done at the Imam Hussein Oncology Centre in Kerbala, Iraq, from July 2022 until December 2022. In this study, 100 female breast cancer patients participated.

**4.1. Inclusion criteria** for patients included at least one measurable lesion greater than 2cm with CT or MRI, adequate organ function, and women with an age greater than 45 years.

**4.2. Exclusion criteria** for patients included Pregnancy or lactation, serious infection, and current alcohol or drug addiction.

**4.3. Data collection:** During the course of the trials, prospective toxicity data was collected. At each patient visit, healthcare professionals and clinical research nurses assessed the toxicities and assigned a grade based on symptoms. At least one dose of the investigational drug was evaluated as part of the HFS evaluation. Medical records and case report forms were used to collect patient initial therapy information, capecitabine compliance data, and safety incident data.

**4.4. Measurement of drug concentration of 5-FU:** Take 5 ml of blood from the patient and put it in an EDTA tube. Then centrifuge the blood and separate the serum. AgNO<sub>3</sub> (20%, 600 µL) was added to a mixture containing human serum (1.0 mL) and the resulting mixture was subjected to a vortex for 3 min and placed to stand for 5 min. NaCl (20%, 700 µL) was added, and the mixture was subjected to a vortex for another 3 min. After centrifugation at 13,000 rpm for 12 min, the supernatant (0.5 mL) was diluted with water to 1 mL in a centrifuge tube and filtered through a 0.22-µm membrane. An HPLC model SYKAM-German with a UV detector was used for the analysis. A C18-OODS column (250 cm, 4.6 µm) was used for separation. The column temperature was maintained at 25°C. The standards and samples were determined using a mobile phase consisting of 5 mM KH<sub>2</sub>PO<sub>4</sub> solution (pH = 6.0) and methanol (96:4) at a flow rate of 1 mL/min. The injection volume was 100 µL. The 5-FU was detected at a wavelength of 254 nm [13].

Figure 1, shows the retention time curve, which represents the duration it takes for a substance to move through the detector from the moment the sample is injected.

**Table 1:** Graded of hand-foot syndrome with symptoms [12].

Grade	Symptoms
Grade 1	Palm and sole paresthesia or dysesthesia
Grade 2	In addition to painless redness or swelling, individuals suffer difficulty when walking or holding objects.
Grade 3	Entails uncomfortable swelling and erythema that inhibits daily activity.
Grade 4	Characterized by skin desquamation, ulceration, and blistering together with severe discomfort.

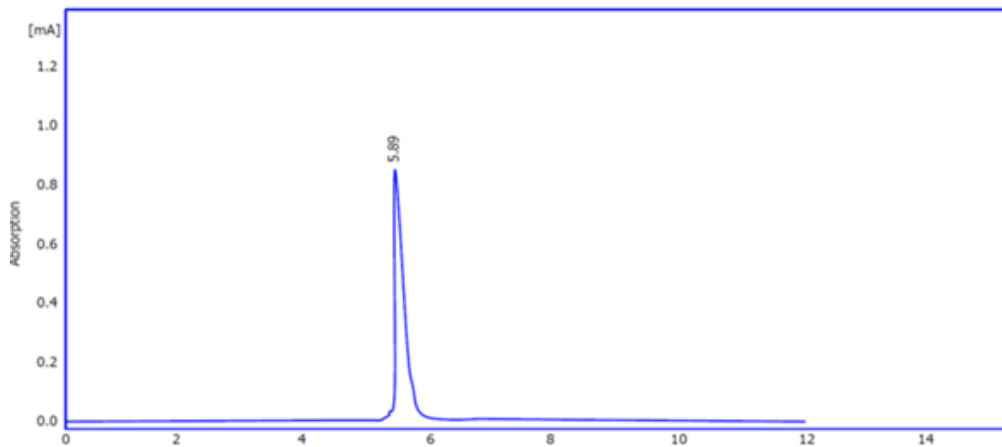


Figure 1: Retention time curves are time required for a material pass from the detector in HPLC device.

### 5. Result

Demographic information regarding the participants collected for the objective of this study shows that: The age range at breast cancer diagnosis was 45–70 years, with a mean of 55.136; and body mass index (26-32); approximately 62% of individuals had a family history of breast cancer, while 86% of married women and 14% of unmarried women had cancer. And approximately 33% of women have left-sided breast cancer, while 67% have right-sided breast cancer. The proportion of patients who underwent surgery (mastectomy, lumpectomy with or without lymph node removal) was 90%; the proportion of individuals with estrogen receptor positivity was 94%; progesterone positivity was only 6%; and 39% of patients in this study had lymph node involvement. The percentage of females who received radiation therapy was 88%, while the percentage of females who did not was 12%. The percentage of patients who received chemotherapy was 92%, while 8% did not, and 53% suffered from hand-foot syndrome, a severe side effect of capecitabine.

Figure 2, shows demographic data of 100 breast cancer patients who participated in this study.

The concentration of active metabolites 5-FU ranged from 301ng/ml to 393ng/ml. Thirty-one percent of patients had a range between 301 and 330 ng/ml, 65% had a range between 330 and 370 ng/ml, and only 4% had a range between 370 and 399 ng/ml. Figure 3 illustrates the plasma concentration of the active metabolite 5-FU in a group of 100 female breast cancer patients who were enrolled in the study.

Figure 4, shows that 53% of patient who participated in this study suffered from hand-foot syndrome whereas 37% of them with grade 1 hand-foot syndrome with symptoms of palm and sole paresthesia, 12% of patient with grade 2 hand-foot syndrome with symptoms of painless redness or swelling, individuals suffer difficulty when walking or holding objects with 4% of patients suffered from grade 3 hand-foot syndrome with symptoms entails uncomfortable swelling and erythema that inhibits daily activity and no patients with grade 4 of hand-foot syndrome. Patients are classified into three groups.

Figure 5, illustrates the incidence of hand-foot syndrome in 100 breast cancer patients receiving capecitabine 53% of them had the hand-foot syndrome, compared to 43% of those without the condition.

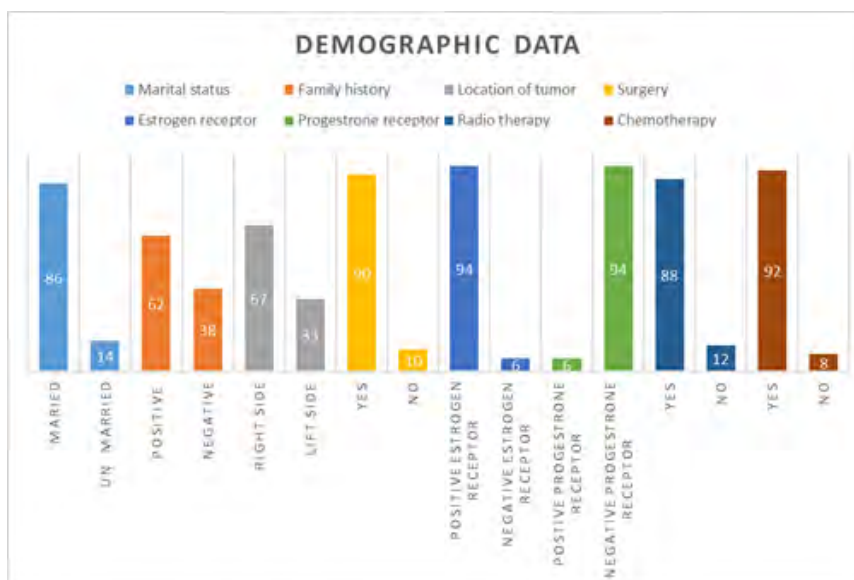
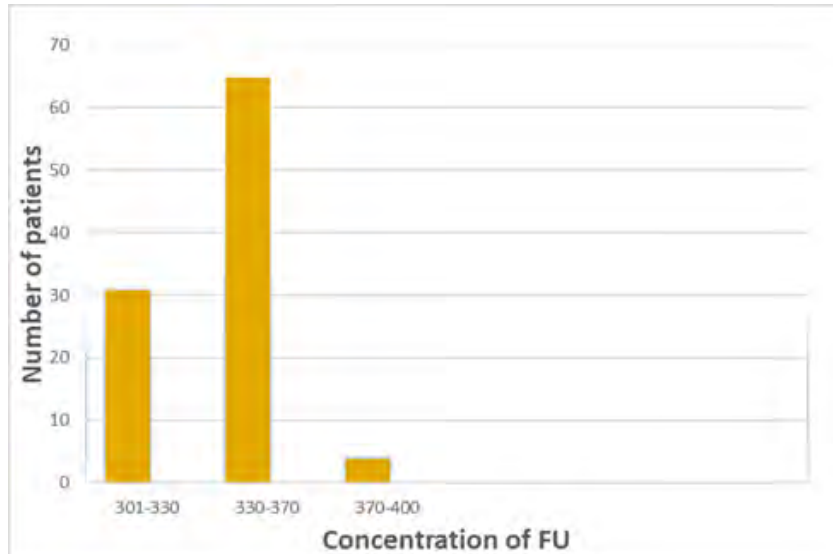
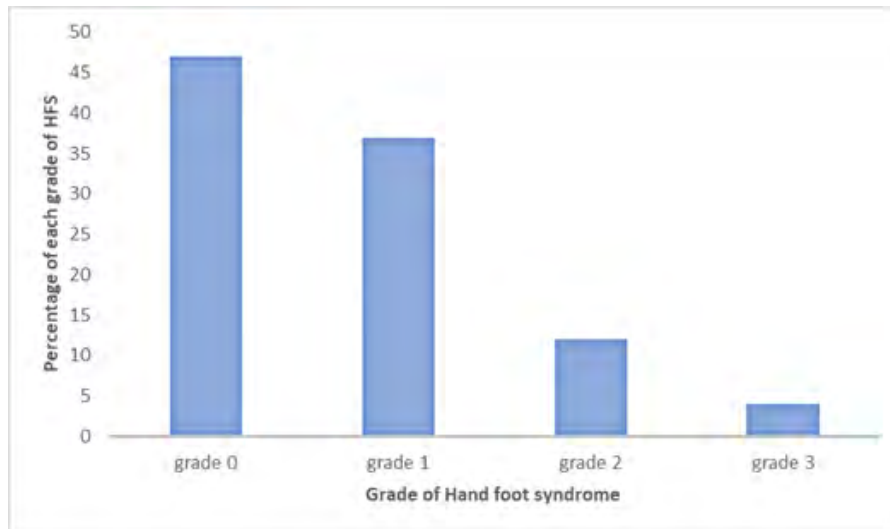


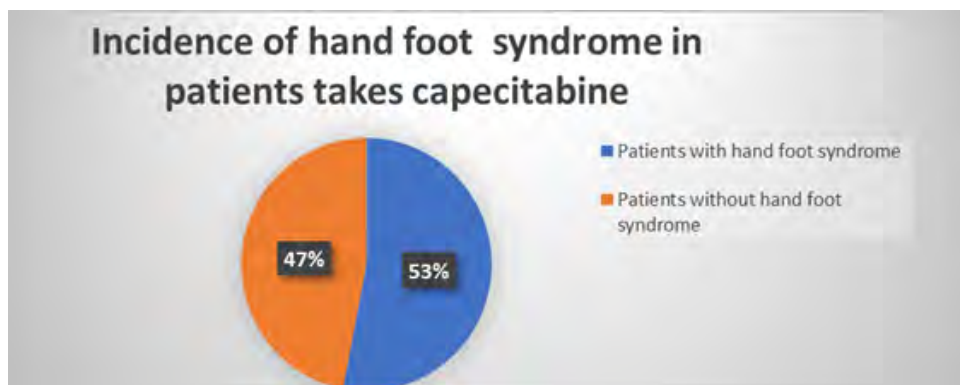
Figure 2: Demographic data of patients who participated in this study.



**Figure 3:** Concentration of active metabolites 5-FU in 100 breast cancer



**Figure 4:** Number of patients within each grade of hand-foot syndrome.



**Figure 5:** Incidence of hand-foot syndrome in patients taking capecitabine.

## 6. Discussion

Through inhibiting the metabolism of fluoropyrimidine nucleosides, capecitabine is a cancer drug used either alone in patients with metastatic breast cancer who have developed resistance to both paclitaxel and an anthracycline-containing regimen or in combination with docetaxel after anthracycline-based therapy has failed [14]. According to the study Lin and in contrast to the stand-

ards of academic research, the average age of the women who gave birth in this study was 55.136 years old. The risk of breast cancer in women under 40 was higher than in older women [15, 16]. Some women develop breast cancer at a younger age (below 40 years), though this accounts for only a small percentage of the overall incidence; however, it was expected that these cases would be diagnosed at a later stage and have a poorer prognosis because they

are combined with more aggressive subtypes. Possible explanations for this observation include the fact that breast development is accelerated in women who reach menarche at a younger age, increasing their risk of developing breast cancer due to prolonged exposure to estrogen. On the other hand, premenopausal women whose menstrual periods begin at a later age have a reduced risk of developing breast cancer. [17]. Several studies have shown that a woman's marital status influences her risk of acquiring breast cancer. Studies have shown that the risk of acquiring breast cancer is much higher in women who have never been married or who have gone their entire lives without marrying [18]. Unmarried women with cancer were found to have a considerably higher risk of presenting with a more advanced stage of the disease than married women with cancer [19]. There are numerous ways for married women with a diagnosis of breast cancer to improve their prognosis for the disease's progression. The actions of the individual are the initial target of this effect. There is a correlation between the marital status of a woman and her health and wellness choices and behaviors. Liu's studies discovered that married individuals were less likely to engage in risky behaviors and more likely to adhere to healthy lifestyle choices, such as eating right and exercising regularly [20]. According to the studies, breast cancer patients with a positive family history were more likely to have the disease than those with a negative family history [21]. A positive family history practically doubles the likelihood that a woman with in situ breast cancer will develop invasive breast cancer [22]. This study found that the concentration of 5-FU in the plasma of patients ranged between 30 and 390 ng/ml, which is consistent with the findings of another study [23] that found the concentration of 5-FU in plasma to be between 290 and 350 ng/ml. Hand-foot syndrome is the most common and painful side effect of capecitabine, making it a significant problem in the treatment of many cancer patients. Little is known regarding the natural history of HFS in capecitabine-containing combination therapy, and HFS has mostly been recorded in individuals who received capecitabine monotherapy. In a previous study by Pharma Development, F. Hoffmann-La Roche Ltd., Basel, Switzerland, and Pharma Development, Hoffmann-La Roche Inc., Nutley, New Jersey, USA, the plasma concentration of FU was between 220 ng/ml and 310 ng/ml. Increasing the concentration above this range will increase side effects like diarrhea and hand-foot syndromes [24].

According to the Janssen study, which found that an individual's projected intracellular concentration of FUTP was a significant predictor of the onset and severity of hand-foot syndrome [25], there is a correlation between the concentration of 5-FU and its metabolites and the occurrence of hand-foot syndrome.

One method used to manage hand-foot syndrome is a reduction in the dose of capecitabine, which proves a relationship between the adverse effects of hand-foot syndrome and drug concentration. In this study, the total HFS frequency was 53%, comparable to

those of earlier research (45%–68%) [26]. This study's total HFS frequency was 53%, comparable to those of earlier research (45%–68%) [27].

## 7. Conclusion

There is a relationship between the incidence of hand-foot syndrome and 5-FU. Drug concentrations in plasma will increase the concentration of 5-FU in plasma, which will increase the incidence of adverse effects of hand-foot syndrome. One way to decrease the incidence of hand-foot syndrome is to decrease the dose of capecitabine, which in turn activates 5-FU.

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