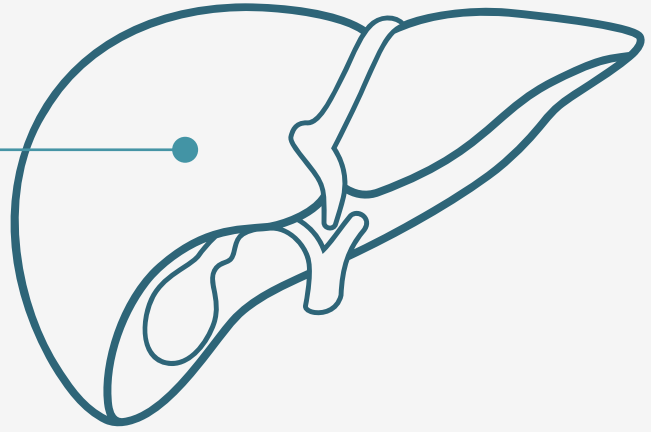


8th Issue

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SASLT NEWSLETTER



Tabel of Content

01

Introduction

Page No. 01

02

Editorial Team

Page No. 02

03

**From function to endurance:
paradigm shifts in advanced
chronic liver disease
prehabilitation**

Page No. 03

04

**Viral hepatitis C
elimination in Egypt**

Page No. 10

05

**Campaign Title: Protect Your
Liver**

Page No. 13

Introduction

Concluding our inaugural year

At the onset of the year, we vowed that the newsletter for 2023 would usher in a new era of scientific research, international collaborations, and valuable insights into the latest developments in our field. I am delighted that we were not only able to fulfill our promises but also exceed them. We have covered a plethora of topics, ranging from the genetics of cholestasis to novel therapies in progressive familial intrahepatic cholestasis (PFIC), as well as the groundbreaking news of the first international clinical trial in PFIC which Saudi Arabia played an integral role. After transitioning to NASH, we proceeded to cover the realm of oncology, exploring new therapies and biological treatments and then moved to the successful story of SASLD annual conference for 2023. Additionally, we had the privilege of hosting the winner of the King Faisal award, who wrote about hepatitis D and made a groundbreaking discovery related to it.

In our recent newsletters, we have extensively covered the prehabilitation of advanced chronic liver and the remarkable story of hepatitis C virus elimination in Egypt. Our goal in 2023 was to distinguish ourselves in terms of scale, authors, and international collaborations. We hope to maintain this momentum in 2024 and surpass our achievements. It is a shared dream within SASLT that this newsletter will serve as the foundation for a future SASLT journal. None of these accomplishments would have been possible without the invaluable contributions of my co-authors, particularly Dr. Saad Al-Ghamdi, who played a pivotal role in organizing international authors and preparing the content. I am deeply grateful to Dr. Saad and indebted to the support and guidance of Dr. Faisal Abulkheil, the president of SASLT, and the entire SASLT board. I also extend my gratitude to the SASLT secretary and everyone else who assisted in the creation of the newsletter, as well as Mr. Diab, whose unwavering support and encouragement pushed us to meet our deadlines. As we approach the end of 2023, I wish everyone a successful year and the very best for 2024. I hope you enjoy and find enrichment in reading our final issue of 2023.

Sincerely,

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From function to endurance: paradigm shifts in advanced chronic liver disease prehabilitation

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Advanced chronic liver disease (AdvCLD) portends severe deconditioning, functional decline and malnutrition (1). Within the last 10 years, physical fitness in AdvCLD has focused on physical frailty and anatomic sarcopenia (5-2), a significant initiative since these conditions are associated with disability and death, independently of the degree of liver failure or portal hypertension (6 7). Although narrowing the focus to study frailty and sarcopenia has been beneficial to the field of exercise and rehabilitation in AdvCLD, novel clinical data necessitates a deeper

understanding of the complex nature of physical fitness in AdvCLD with a wider view on its pathophysiology and multisystemic implications (8). Within the field of liver transplantation (LT), such change in paradigm is particularly logical given the inherent need to achieve longer survival while co-managing cardiometabolic comorbidities. Herein, we propose a shift in paradigm where physical fitness takes priority over function and frailty, as critical in the success of LT and provide a coherent prehabilitation approach for potential candidates.

The framework of physical fitness

Physical fitness has been defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies" (9). Such definition perfectly aligns with the aim of LT, which is to eliminate a life-threatening liver disease so that recipients can regain their autonomy and role in their community. Understanding these concepts is paramount prior to embarking in training LT candidates with AdvCLD (i.e., prehabilitation). Is it function and degree of frailty that will help determine success in LT or is it endurance / fitness? In other words, is the goal of prehabilitation to gain sufficient mobility and function to undergo LT or should it be to improve a recipient's health and physical fitness to maximize transplant potential and outcome from their gift of life?

LT candidates and recipients need to be physically fit in order to traverse the different stages of transplantation, from AdvCLD and candidacy to post-LT status, with its associated chronic illnesses. Comprehensive prehabilitation focused on physical fitness works beyond mobility and function (i.e., physical frailty) and includes muscle strength and endurance, and cardiorespiratory fitness (CRF) or aerobic endurance (Figure 1). CRF is one of the strongest predictors of mortality, as it potentially carries more significance in outcome than established risk factors such as smoking, hypertension, hyperlipidemia or diabetes (10). Cardiopulmonary exercise testing (CPX) is the reference standard to assess CRF (11). Although poorly utilized in AdvCLD, our group recently showed that LT candidates have a poor CRF, comparable to that of heart transplant candidates (Hughes et al, submitted). Further, poor CRF from CPX is associated with waitlist mortality and does not improve spontaneously following LT (12,13). Consequently, in most cases post-LT rehabilitation is required(15,14)!

Building a prehabilitation program for LT

Prompt diagnosis of deconditioning or of any of its phenotypic manifestations such as physical frailty or anatomic sarcopenia, are necessary to identify potential LT candidates in need for prehabilitation. Although there are multiple tools and endpoints to identify physical decline, most frequently used are shown in Table 1 (17,16,12,3). The 6-minute walk test (6MWT) and the liver frailty index (LFI) are the most studied tools, and deconditioned candidates walking <250 m during the 6MWT or frail candidates achieving an LFI score ≥ 4.5 have a 2- to 3-fold increase in waitlist mortality (16,6,3). Importantly, in such cases posttransplant mortality is only mildly increased, if at all. However, poor physical fitness is associated with a longer hospital stay and a decreased rate of discharges to home on LT hospital admission (i.e., discharge to rehabilitation or skilled nursing facility) (20-18). Thus, when considering the value of prehabilitation and whether it is financially sustainable, factors that need to be considered are the number of patients not waitlisted for LT, the number of candidates dropping off the list due to frailty or disability, and the resources invested in posttransplant care. Since prehabilitation is expected to increase the number of patients receiving a transplant while reducing healthcare utilization (both pre-LT and post-LT), the benefits would potentially outweigh the investment in prehabilitation and make it a financially sustainable program.

Whether prehabilitation can sustain post-LT physical activity and translate into improved long-term survival by maintaining improved CRF is a matter in need of further study.

At our center, we obtain the LFI in all LT referrals. The results are discussed at the LT Selection Committee, which has allowed all faculty and staff to become familiar with these assessments and to appreciate the benefits of prehabilitation. All patients (potential or waitlisted candidates) with an LFI >4.2 are then referred to our Prehabilitation Clinic (Figure 2) where a specialized team provides fitness and nutritional assessment, physical literacy, a refined exercise prescription and training adherence monitoring. At this clinic we measure both the 6MWT and LFI at each visit, which can occur at intervals of 1 to 8 weeks, depending on the needs of each candidate. The nutritional assessment incorporates the phase angle from bioimpedance spectroscopy as a metric for malnutrition and sarcopenia (7); dietary recommendations are adjusted at each clinic visit based on results. The exercise prescription is a critical component of our pre transplant assessment and for most patients it consists of a home-based exercise program tailored to available resources (Table 2). During follow-up visits, exercise professionals evaluate adherence to the intervention and adjust it accordingly. Most importantly, patients and their caregivers are interrogated for exercise barriers or their facilitators, and troubleshooting strategies are provided to incentivize exercise and physical activity. We follow a behavioral counseling model, incorporating techniques such as motivational interviewing, and each clinic finalizes with an updated exercise prescription negotiated in agreement with patient and caregiver. All is done within the context of a standardized multidisciplinary institutional protocol (Prehabilitation and Nutritional Therapy in Liver Transplant Candidates).

Learning the trajectory of the 6MWT or LFI is key to understand the physiologic reserve of each transplant

candidate (21). Based on data from a cohort of over 1200 patients assessed at a prehabilitation clinic, we now know that an improvement in LFI by at least 0.4 denotes training engagement and carries a survival advantage for waitlisted candidates (Lin et al, submitted). In frail individuals for whom disability is being considered a contraindication for LT, we use an interval improvement by 0.4 in LFI as an indication for transplant readiness, irrespective of the degree of frailty. In this way, we utilize frailty metrics as a tool to direct our prehabilitation of individuals and in an attempt to recover their LT eligibility status, and not as a tool to deny transplantation to patients. Our center no longer utilizes self-reported metrics of frailty (e.g., Karnofsky or ECOG) given their subjectivity and lack of understanding of their trajectory with physical training (5). To date, in transplant candidates, only the peak oxygen consumption (VO_{2peak} from CPX), 6MWT, LFI and short performance physical battery have shown to be sensitive to change following an exercise intervention (22).

Incorporating fitness and healthcare information technology to prehabilitation

Unlike heart and lung transplant programs, for which prehabilitation is considered vital for transplant eligibility and survival, LT programs have no direct means of prehabilitating their candidates. The physical fitness (or CRF) culture is still underdeveloped in the LT field, as witnessed by our current model where rehabilitation can only be offered once disability is identified during a hospital stay (i.e., inability for self-care, either before or at LT). In order to overcome such cultural (and financial / third-party payor) barriers, some groups have resourced to using fitness and healthcare

information technology to support the prehabilitation agenda. The Exercise & Liver Fitness (EL-FIT) is a smartphone application created to provide physical literacy, tailored exercise training, and monitoring of adherence (23). Through gamification features, EL-FIT also aims to motivate patients to exercise and become physically active. When paired to a personal activity tracker (i.e., Fitbit or Apple Watch) it becomes a powerful tool to monitor training adherence. Finally, a group support function allows EL-FIT participants to encourage one another. We recently showed that a mobile-assisted home-based exercise program allowed transplant candidates to improve their 6MWT by 41 m and LFI by 0.4. Subjects were strictly monitored for training adherence through healthcare information technology built into EL-FIT, and at their maximum effort daily steps increased from 1260 to 3508 (24). This is an attestation of physiological reserve and self-efficacy for training in AdvCLD.

Other virtual resources have proven to be effective in training or improving dietary habits among patients with chronic liver disease (25). The “Wellness Toolbox” (www.wellnesstoolbox.ca) also offers exercise and dietary interventions designed for patients with AdvCLD.

Combining prehabilitation and living donor liver transplantation

One of the concerns of prehabilitation is whether the improvement in physical fitness will be sustained enough to allow waitlisted patients to reach LT with improved physiologic reserve. Exercise research in other fields of study have clearly shown that the benefits are not sustained but rather lost after training is stopped (26). Living donor LT offers the possibility of planning for exercise training and transplant surgery in sequence. In other words, with deceased donor LT

the unpredictability of the organ offer could make the LT window to close prior to organ availability, whereas with living donor LT the surgery can be scheduled for the time of peak physical performance and training benefits (Figure 3). Such model can both maximize the pool of recipients while minimizing healthcare utilization.

Conclusions

The constructs of frailty and sarcopenia represent the tip of the iceberg within a more complex conceptualization of physical fitness. Further advancement in prehabilitation for AdvCLD necessitates a shift in paradigm towards a more holistic approach that prioritizes deconditioning or fitness. It is only through such widening of focus that encompasses all components of physical fitness that the field of prehabilitation (or rehabilitation in non-LT candidates) will continue to grow. A strategy emphasizing endurance over function is expected to impact not only on making patients transplantable, but on improving post-LT morbi-mortality and quality of life through the betterment of physiological reserve and specifically CRF. Clinical trials with clear endpoints and reproducible interventions that make use of novel fitness training and monitoring technology are needed to further the field.

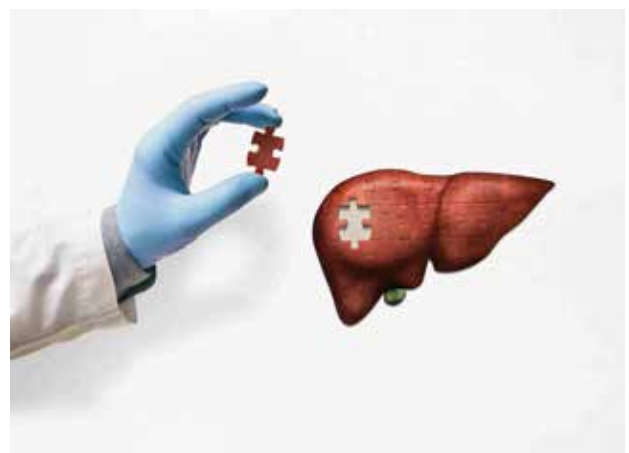


TABLE 1: Physical fitness toolbox for liver transplant candidates.

	Severe Physical Decline	Moderate Physical Decline	Mild / No Physical Decline
Live frailty index	≥ 4.2	3.1 - 4.1	≤3.2
6-minute walk test	< 250 m	250 to <450 m	≥450 m
Daily step count	<1200 steps/day	1200 - 5000	>5000
VO _{2peak} (from CPX)	< 60%	≥ 60%	

TABLE 2: Types of exercise prescription with varying intensity.

Program	Description	Patient Example
Inpatient Rehabilitation	Supervised program	Bedbound or wheelchair
Facility-based outpatient PT	Supervised program	At risk for falls or in need for assistive devices for walking
Intensive HBEP	Independent or facilitated by caregiver	Frail to pre-frail and able/willing to follow training instructions
Home-health PT	Visit by PT, as covered by insurance	Frail to pre-frail with no support to follow HBEP
Maintenance program	150-200 min/week of moderate intensity training	Robust or fully independent

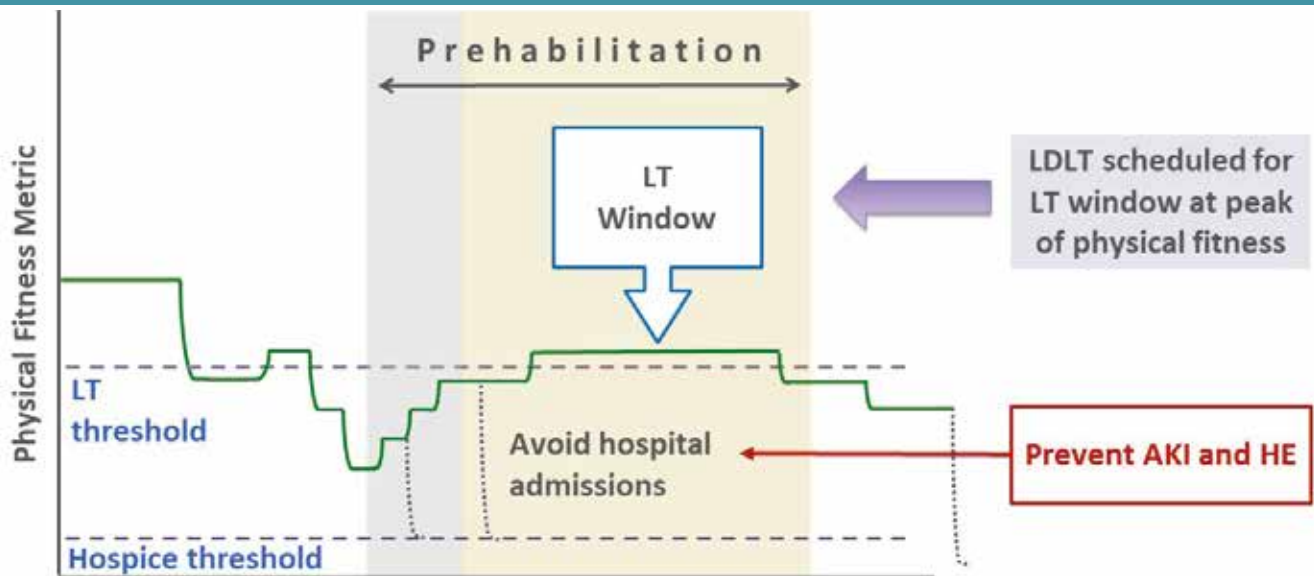
HBEP: home-based exercise program. PT: physical therapy.

Figure Legends

FIGURE 1: Holistic view on physical fitness and its components.

FIGURE 2: Prehabilitation clinic workflow.

FIGURE 3: Transplant window in prehabilitated liver transplant candidates.



Potential candidates considered to be too deconditioned to undergo liver transplantation (LT) should be referred to a prehabilitation program to improve their fitness. Since the benefits of prehabilitation are expected to wear off following completion of training, pairing living donor liver transplantation (LDLT) to the window of peak physical fitness and maximum physiologic reserve would be of particular benefit to both patients and LT programs. During prehabilitation it would be important to avoid hospitalization, commonly in relation to hepatic encephalopathy (HE) and acute kidney injury (AKI), by providing best medical practices through a dedicated prehabilitation clinic. Hospital admissions can be associated with a severe physical decline below the threshold where providers would consider hospice care.

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Viral hepatitis C elimination in Egypt

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Hepatitis C virus (HCV) infection is a significant public health problem and a major cause of liver-related morbidity and mortality that challenges healthcare systems in many countries. Historically, Egypt is one of the world countries with the highest prevalence of HCV infection. This extraordinary prevalence of HCV in Egypt is primarily due to the long-lasting treatment campaigns against schistosomiasis using parenteral therapy conducted by the Egyptian Ministry of Health (MOH) during the period from 1980–1950.

To combat such an epidemic, the Egyptian MOH launched in 2006 the National Committee for Control of Viral

Hepatitis (NCCVH) to manage the HCV epidemic in the country. The journey from having one of the world's highest rates of hepatitis C infection to being on the path to elimination has passed through several well-organized steps or phases.

Phase 1: Interferon Treatment for some:

During this phase, 23,2014–2006 national centres for HCV screening and treatment were established. PEGylated interferon was provided for 45000 infected people every year. By the end of this period, 350000 people were treated with a cure rate (SVR) < 60%. Unfortunately, a large number of patients were ineligible for treatment.

Phase 2: Direct-acting antiviral agents (DAAs) treatment for all:

During this period, the NCCVH centres increased from 23 to 46 centres throughout the country. DAAs were provided initially for patients with advanced fibrosis and cirrhosis, then for all patients without prioritisation. DAAs' negotiation regarding the reduction of brand price and generic productions was achieved. In 600,000, 2016 patients were treated by DAAs with a cure rate (SVR) > %90 and the waiting lists for DAAs were entirely terminated.

Phase 3: Targeted screening for HCV in Egypt:

During this phase, families of HCV patients, healthcare providers, prisoners, students admitted to universities, patients attending intervention procedures in hospitals and blood bank donors were screened for HCV infection. From August 2016 to August, 2017 3,300,000 subjects were screened for HCV. Near 300,000 people were positive for HCV antibody, %86 of whom were HCV RNA positive and in need of treatment. By the middle of 2018, more than 2 million patients were treated for HCV. Epidemiological studies show that, in addition to those who have already been treated, there are about 3 million individuals with undiagnosed HCV infection in Egypt. This pool of undiagnosed individuals, if untreated, is at risk of progressive disease and is a potential source of infection over the coming years. This led to the innovation of the Egyptian presidential initiative (100 million Seha).

Phase 4: HCV screening for all populations:

On October 2018, the Presidential initiative to eliminate hepatitis C (100 million seha) was released to

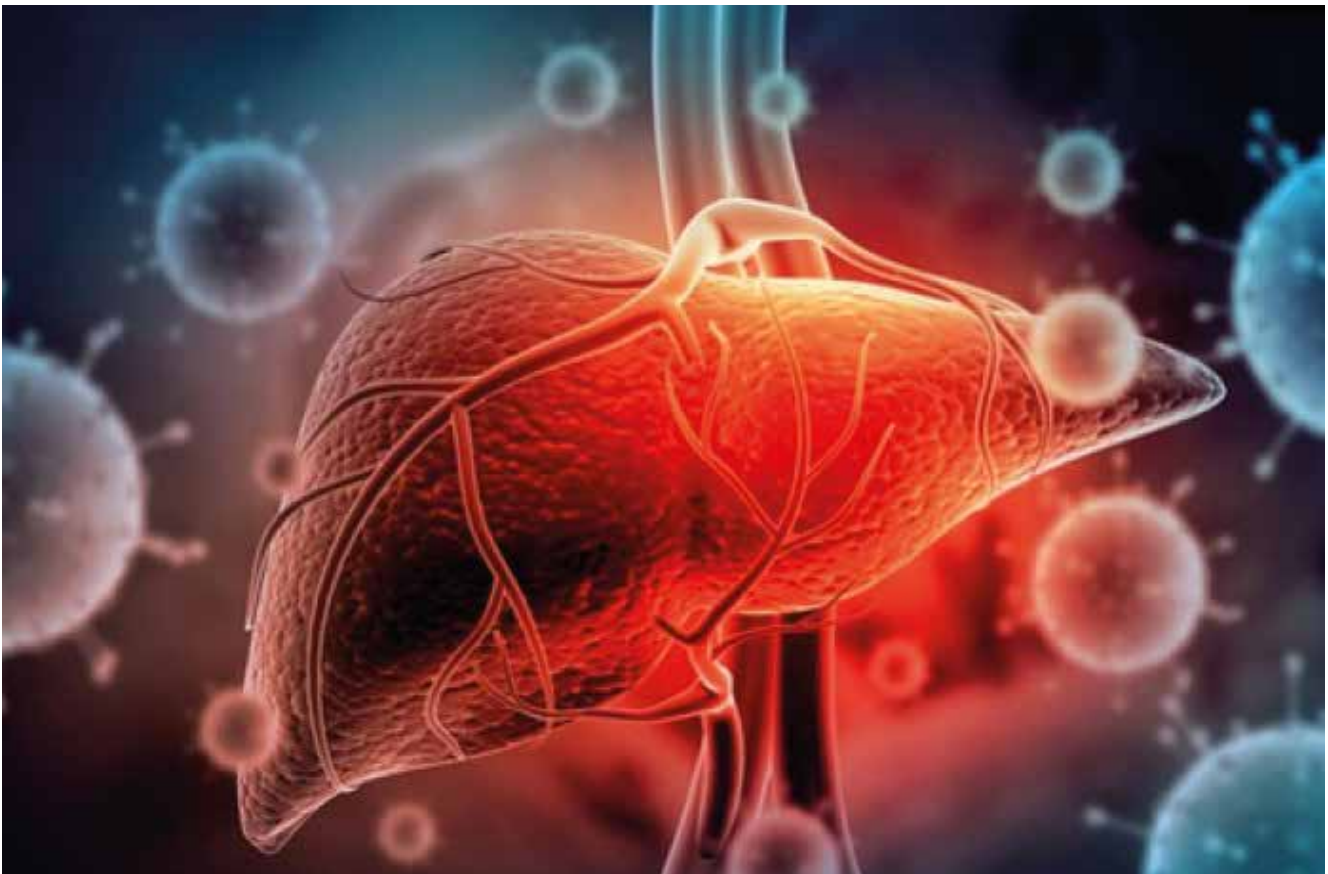
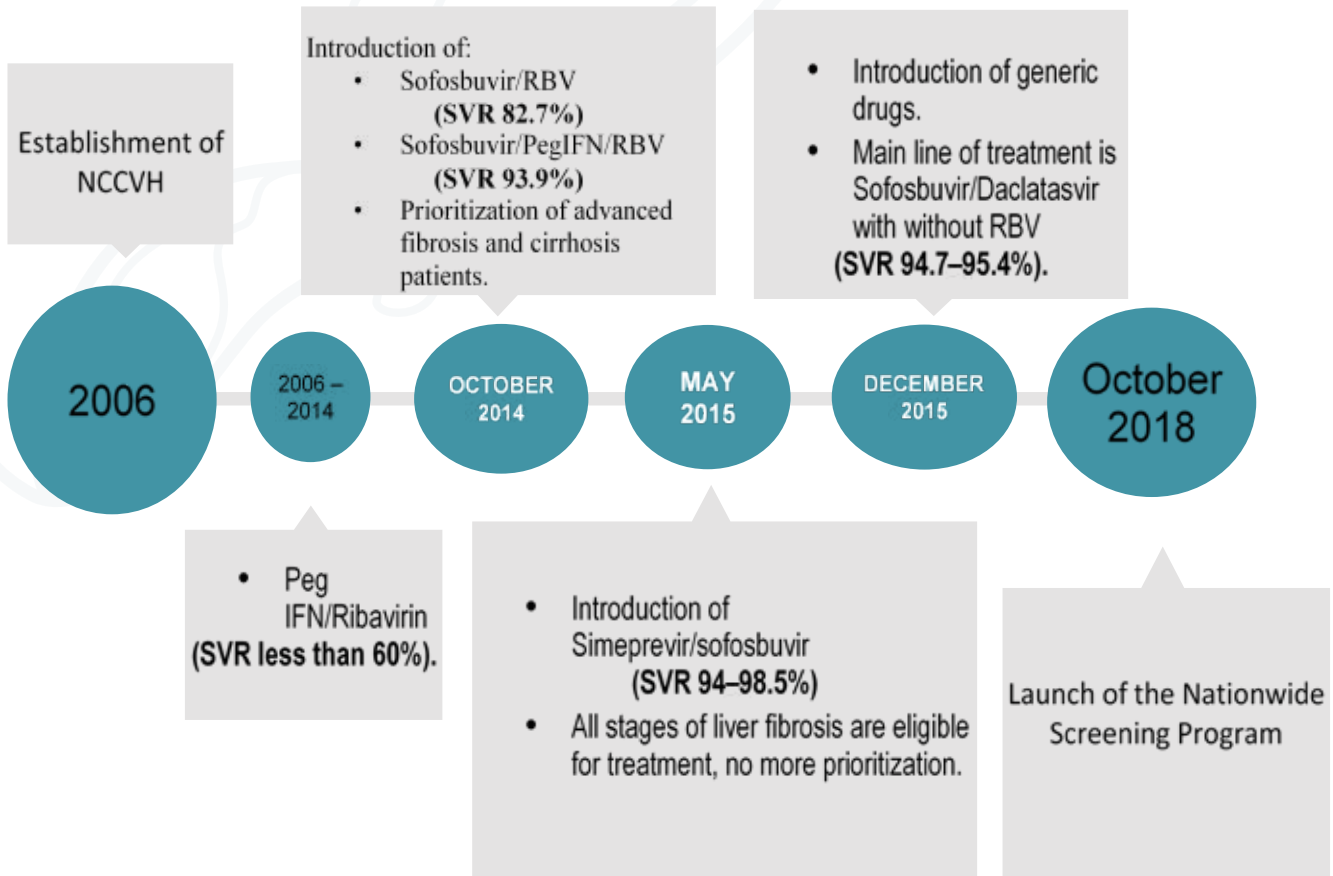
provide free testing and treatment for hepatitis C infection. Near six thousand testing sites and 165 treatment centres were opened to achieve this strategic national mission. This national campaign tested over 60 million people and provided DAAs treatment for more than 4.1 million people.

In 2022, the MOHP conducted a household survey in 27 governorates via a multistage cluster sampling technique. RT-PCR confirmed patients with positive anti-HCV specimens. The Survey revealed that HCV RNA prevalence dropped to %0.38. Egypt is now best positioned to focus on the "micro-elimination" approach as the national macro-elimination response to HCV has met most of the criteria required for employing this approach.

In October 2023, The World Health Organization (WHO) congratulated Egypt for its extraordinary success in eliminating hepatitis C. Egypt is the first country to reach "gold tier" status on the WHO's path to hepatitis C elimination.



Steps on the path of HCV elimination



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Campaign Title: Protect Your Liver

Report on the implementation of the Protect Your Liver campaign

In line with the objectives of the Saudi Society for Liver Diseases and Transplantation (SASLT) and from the standpoint of community awareness and the role of effective participation of relevant parties in it, the Society, in unique cooperation with the Health Affairs of the Ministry of the National Guard Hospital (MNGH), represented by the Department of hepatology and Liver Transplantation and the Department of Internal Medicine, organized an awareness campaign entitled (Protect your liver) (احم كبدك) from November 2023, 4-2,

The Aim of this campaign is to address the misuse of herbs, nutritional supports, medications and all metabolic related liver disease mainly those related to diabetes mellitus and obesity and dyslipidemia as they are a prevalent issue in our community, that can have an adverse

effect on both the liver and kidneys. As part of our campaign, we strive to educate the community about the potential risk of using herbs, nutritional supports used by athletes, medications namely misuse of antibiotics, alcohol and all metabolic related liver diseases (MASLD).

The preparation:

for this campaign it took us almost 2 month My self and an outstanding group of medical students from King Saud University for Health Science, we held several meetings in our hospital at (MNGH), from brainstorming ideas, to choosing the topics and subjects needed to be addressed in this campaign, to ultimately how to choose the most relevant brochures for each topic we need to address.

Then we consulted the SASLT about all these ideas and topics we elected to

choose and with full generous financial and scientific support from the SASLT, we made everything that we needed to have this successful campaign (including posters, brochures, TV screen, and all known social media).

We divided our teams to groups; each group will take care of one segment and we distribute them all need tool to be able to deliver their ideas

Area of the campaign

The first day (Nov-2) campaign started in all area of outpatient Ministry of the National Guard Hospital targeting patients and their accompanies, we also target the nurses and medical staff who usually dispense these medications or deal with the patients. then in the second and third days (Nov-4-3) the campaign continued its active, distinguished and effective presence in the Roshan front (Riyadh front), which was well received by heavy and distinct presence of all visitors and fulfilled their aspirations due to the information presented and answers to their questions orally by myself and my groups also through the presentations both alive and through recoded media prepared prior to the campaign then we display it on TV screen , with that also we distribute brochures that were provided for the purposes of the campaign.

At the conclusion of the work of this campaign, I would like personally and with my working group to extend our sincere thanks to the Saudi Society for Liver Diseases and Transplantation (SASLT), the sponsor of this campaign, whose unlimited support contributed to the implementation of the activities of this campaign with ease and ease and contributed to achieving the set goals. Our thanks go to the Ministry of the National Guard Hospital (MNGH), the planner, organizer, and implementer of this campaign. For its effective cooperation, which made this experience of this unique joint work and effective cooperation a model to be emulated in the future.

Also sincere thanks to my team headed by Dr. Shaden Aldalaan and all her colleagues, for their dedicated outstanding work, that made this campaign go from myth to a reality.

We look forward to more of this fruitful and effective cooperation between the relevant authorities in the future to raise the level of our aspirations to keep pace with our vision based on the ambitious 2030 vision that seeks to raise the level of community awareness in a way that contributes to reducing liver diseases and the resulting complications and deaths and in a way that achieves the promotion of health in the Kingdom and makes it compete with other countries. advanced in this field.





SASLT future scientific events



SASLT

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Saudi Society for the Study of Liver Disease
and Transplantation

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